Mandate under article 75(1)g of the BPR concerning ”Evaluation of the level of the risks for human health and for the environment of DBNPA used in biocidal products of product type 4”

Content

1. Background for the mandate

The BPC opinion on the active substance DBNPA in product type (PT) 4 was adopted during the BPC-31 in June of 2019. The representative use of DBNPA in PT4 is the disinfection of food vessels and machinery. The disinfected food vessels could be bottles or processing vessels.

The BPC concluded that "*The risk assessment showed no unacceptable risks for DBNPA for humans and for the environment including the environmental relevant metabolite CAM. DBNPA is considered to have endocrine disrupting properties relevant for both humans and non-target organisms in the environment. However, there is no currently agreed methodology for undertaking a risk assessment for human health based on such properties and no agreed methodology available on how to consider the data used for the identification of whether this substance is an endocrine disruptor in risk assessment for the environment. Given the rinsing step of DBNPA treated bottles does not exclude the presence of DBNPA residues in the bottles after rinsing and given that release to the environment of DBNPA occurs via waste water, a risk related to the ED properties for the general public and the environment cannot be excluded.*"

The BPC concluded that DBNPA is considered to have endocrine disrupting properties for humans and non-target organisms, mainly based on data on mammalians. The assessment followed the *Guidance for the identification of endocrine disruptors* (ECHA and EFSA, 2018).

On July 8 2020 the European Commission submitted to the European Chemicals Agency (ECHA) a mandate according to article 75(1)g of the Biocidal Products Regulation (EU) 528/2012 (BPR). The mandate requests the opinion of ECHA on the risks associated with the endocrine disrupting (ED) properties of DBNPA from the use in PT4.

During the BPC-36 in October 2020, Denmark was appointed the rapporteur for this mandate.

2. Data collected and used in the opinion

For the work on the mandate, information was obtained from several sources. The applicant for the approval of DBNPA in PT4 was contacted for information and informed the Danish Environmental Protection Agency that they did not intend to submit information, but considered a newly established consortium on bromine to be in a better position to submit the information requested by the Danish EPA in relation to this mandate. The applicant did submit an exposure assessment based on the representative uses in the PT4 CAR. The consortium consists of several parties within the bromine industry and contacted ECHA directly in December of 2020 to advise that they wished to submit information related to this mandate. They were instructed by the eCA to submit information obtained through a systematically performed literature search based on the recitals of the mandate.

ECHA established contact to the European Medicines Agency (EMA) to obtain relevant information on use of bromine in medicines, as well as to the NL CA, who are the eCA for several biocidal active substance/PT combinations with active bromine.

Due to the time constraints of this mandate, the eCA agreed with the consortium to have continuous submission of data, dependent on the recitals of the mandate. Therefore, on March 1 2021, the consortium submitted the data they intended to use in their assessment, including a literature search. Additional data was submitted on April 8 on the request of the eCA. On April 16 2021, the consortium submitted their draft assessment concerning the threshold for ED properties for human health and the environment. On April 30 2021, the applicant for DBNPA in PT4 (Nutrition & Biosciences (Switzerland) GmbH) submitted the draft exposure and risk assessment from use of DBNPA in PT4. The submitted data and assessment is available to the EU Member State Competent Authorities.

The first draft assessment was submitted to ECHA by the eCA on May 10 2021. ECHA then launched an e-consultation with the other Member States with a commenting deadline of June 18 2021. The first draft assessment was also presented for a first discussion in the Working Groups during WG-II-2021 in June 2021. The comments received from the other Member States were taken into consideration for the revision

of the assessment prior to WG-III-2021. Furthermore, the applicant and the bromine consortium were given the opportunity to submit any input they might have on the questions and comments received by the eCA on the first draft assessment. The draft final assessment was submitted to ECHA by the eCA on August 20 and discussed at WG-III-2021.

3. Setting a threshold for endocrine disruptive substances –in general

Several uncertainties exist related to risk assessments of ED substances. The four main uncertainties related to both the environmental and human risk assessment are 1) The existence of thresholds, 2) Lack of studies with exposure during sensitive windows 3) Limited sensitivity of many regulatory testing methods with regard to relevant endpoints addressed 4) The non-monotonic dose relationship of endocrine disrupting chemicals (Hass et al., 2019). Additionally, for the environment 5) the uncertainty of the impact of adverse effects on population level (Matthiessen et. al., 2016). It should be noted that uncertainties related to ED risk assessment are not limited to the five listed, and several others exist (JRC, 2013).

1. In the scientific literature, there is debate about whether or not a threshold exist for endocrine disrupting effects of a substance (Matthiessen et. al., 2016; Borgert et. al., 2013; Brescia, 2020; Day et. al., 2018; Lamb IV, et. al., 2014; JRC, 2013).

   On one hand, it is argued that a threshold for such effect must exist, based on knowledge of the endocrine homeostasis and control (Borgert et. al., 2013; Brescia, 2020; Lamb IV, et. al., 2014). On the other hand it is argued that the same homeostasis of the endocrine system is the reason to why no threshold can be determined, specifically considering that low doses of endogenous hormones are present and fluctuating in the body and therefore, small additions (or subtractions) to their actions will have a significant impact, especially in the developing organism where hormones play a significant organizing role at a time where homeostatic control is not effective/developed (Hass et al., 2019; JRC, 2013; Endocrine Society, 2018; Demeneix et al., 2020; KemI, 2013).

2. Exposure during early development can lead to irreversible effects as they are the main drivers in physiological development of the organism. The adverse effects following a disruption in the hormonal system during development will however most likely not be present at this time but will manifest later in life. There is currently no studies correlating the endocrine activity during development and late adverse effects following this. While this may not be necessary in the ED hazard assessment, it would be very difficult to assess level of risk (JRC, 2013; Endocrine Society, 2018; Demeneix et al., 2020; Even Chorev et al., 2020).

3. From June of 2018 has it been mandatory to assess biocidal active substances for their ED potential according to criteria established in Commission Delegated Regulation (EU) 2017/2100 of 4 September 2017 setting out scientific criteria for the determination of endocrine-disrupting properties and the *Guidance for the identification of endocrine disruptors* (ECHA and EFSA, 2018) in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009. Standard information requirements under BPR have not been designed to identify the potential for ED properties and as such the (initial) assessment of ED is limited to studies without sensitive endpoints. The information requirements was updated to include ED sensitive endpoints in Commission Delegated Regulation (EU) 2021/525 of 19 October 2020 which means that only from this point on, specific relevant information on ED sensitive endpoints are mandatory. This is of particular importance not only in the hazard evaluation of ED, but also in the risk assessment of ED active substances. It may be possible to identify a substance as ED based on apical[1] endpoints, but considering that a threshold of adversity should be assessed in the risk assessment it is very difficult without ED adverse endpoints. At present, almost no active substance dossiers include studies with relevant adverse endpoints to base the risk assessment on. Determining which

[1] Apical= endpoints acting as surrogates for the actual endpoints, e.g. thyroid hyperplasia is an apical endpoint used in the assessment for adverse effect of (among others) neurodevelopment.

endpoint(s) to base the risk assessment is crucial (JRC, 2013; Endocrine Society, 2018; Demeneix et al., 2020).

4. In the scientific literature, there is also debate on how to account for the non-monotonic dose-response relationships (NMDR) of endocrine disrupting chemicals in a risk assessment as standard regulatory studies are not designed for this purpose (Matthiessen et al., 2016, Hass et al., 2019, Vandenberg et al., 2012, Hill et al. 2018).

5. Specifically for the environmental risk assessment, Matthiessen et. al. (2016) argue that the link between endpoints and the relevance for population level should be better understood before it is possible to conduct a risk assessment. The paper lists a series of considerations about the data package to be taken into account before an environmental risk assessment would be considered appropriate for the non-target organisms, e.g. sensitive species/life cycles, delayed effects etc. Some experts also consider that current standard tests do not adequately cover the sensitive endpoints in order to protect populations in the environment (JRC, 2013).

Given that bromide is an essential trace element for human (and animal) life, a natural threshold of adverse effects must exist. Below this threshold of toxicity the biological response in the human body will be beneficial (or adaptive). As bromide is found naturally in the environment, similar considerations of the existence of a threshold as for the human life can be made.

There is no scientific consensus on whether or not a risk assessment can be conducted for substances with ED properties. Based on the information available to the eCA, it has not been possible to establish a threshold for adverse effects for bromide in mammals or for other the non-target organisms.

Furthermore, in the opinion of the eCA that additional uncertainties to the risk assessment also exist, e.g.:

a) use of safety/assessment factors to account for uncertainties: to which degree can safety/assessment factors account for data gaps? Almost no research exists related to the differences in sensitivity of ED effects between the developing and fully-developed individuals, a safety/assessment factor would not be based on scientific documentation,

b) use of animal models for humans, especially using these for the thyroid modality considering that humans are cognitive superior to animals and thyroid hormones are responsible for the neurodevelopment,

c) consideration of adversity. Hormone disruption leads to continuous degrees of adverse effects, when should these effects be considered adverse?

d) use of apical endpoints as surrogates for the actual adverse effects in a risk assessment. E.g. thyroid hyperplasia can act as a surrogate for decreased neurodevelopment for the ED hazard assessment, but can this be used for setting a threshold of adversity when not knowing the actual neurodevelopmental impairment and control of the thyroid homeostasis?,

e) consideration of the increase in prevalence of diseases related to the endocrine system in humans. Should consideration of this be disregarded or included in the risk assessment, considering that these diseases are not just present within a sensitive minority of the population?

f) how data from the ED hazard assessment for human health can be used in a risk assessment for non-target organisms in the environment (for substances where the ED for ENV is based on the data package for HH).

4. Risks for human health

4.1 Setting a threshold - section 10(a) of the mandate

A biological threshold of thyroid toxicity from exposure to bromide must exist due to the points stated for

bromide in section 3. The further evaluation is aimed at determining whether or not this threshold can be quantified for use in a quantitative risk assessment.

For the human health assessment, several repeated dose, reproductive and developmental toxicity studies were available with NaBr, NH4Br, KBr, HBr, LiBr and Br2 in rats, mice, dogs and/or humans including a recent guideline compliant 90-day repeated dose toxicity study (OECD TG 408), a 2-generation reproductive toxicity study (OECD TG 416), and a pre-natal developmental toxicity study (OECD TG 414) with NaBr in rats. Several studies aimed at identifying mechanism of action of NaBr and KBr in rats and dogs were also considered.

It should be emphasised that no hazard assessment of the endocrine effects in the available studies has been performed by the eCA, as this has already been performed. Please refer to DBNPA PT4 Assessment Report and DocIIA for details on this. Most of the studies available for the work on the mandate are identical to those available for the hazard assessment.

In trying to evaluate whether or not a quantifiable threshold can be set for bromide's thyroid disrupting properties, the following different aspects has been evaluated for human health by the eCA:

1. Species-specific physiology of the thyroid hormonal system in order to evaluate whether or not information from the submitted rat and dog studies can be used to set a quantifiable threshold of thyroid-mediated toxicity in humans
2. Iodide- and chloride status in the human body and their impact on threshold for bromide thyroid toxicity in order to investigate if a possible biological threshold of thyroid toxicity is static or depends on the presence of other halogens
3. Sensitivity of the endpoints in the submitted studies and whether or not the resulting NOAELs from these studies can be used as Point of Departure for setting a quantifiable threshold at which no risk of thyroid-disrupting adversity can be expected
4. Subclinical hypothyroidism in humans and the relevance in setting a threshold of toxicity
5. Cf. section 3 regarding the uncertainties for setting a threshold for endocrine disrupting effects in general.

1. Species-specific physiology of the thyroid hormonal system

There exists several differences in how the thyroid hormonal system functions between species. This aspect was discussed during the ED hazard assessment of DBNPA and will not in detail be discussed for this mandate, but is summarised here: Between humans and rodents there is a difference between the amounts of stored thyroid hormones (TH) in the thyroid gland as well as the level of transport proteins in serum, where the adult rat only stores these for a few days in contrast to adult humans who can store up to several months. In addition, rodents do not have thyroid binding globulin (TBG). This results in a higher level of TH in serum of which could be readily available for metabolism and excretion. Therefore, the TH level in rodent serum may decrease earlier than in adult humans. However, considering the sensitive time period in humans, and that the t4 serum half-life is also only a few days in neonates as well intra-thyreoidal storage of neonates is similarly low, neonates would be expected to also a have an earlier decrease in serum TH levels than adult humans and are therefore more sensitive to a shorter period of exposure. However, and maybe even more importantly, there is little knowledge of the species-specific differences in clinical impact following changes in thyroid hormone levels. Specifically, considering the essentiality of the thyroid hormones for development in especially the nervous system and the fact that humans are cognitive superior to rats, a small change in thyroid hormone levels in humans may have more substantial effects in developing humans than in rodents.

Considering that the only available human study on the correlation between bromide intake and thyroid hormone levels was performed in adult healthy volunteers (and therefore a comparison between effects in sensitive human populations not available), it was concluded by the eCA that these differences should not disregard the use of rat and dog models for evaluating the thyroid disrupting potential in humans. In addition, a few studies in humans show that bromide plays a (unknown) role in thyroid disease.

For the above-stated reasons it is difficult to establish a quantifiable threshold based on animal studies when considering both the species-specific differences in impact on thyroid hormone level and possible differences in how changes in thyroid hormone levels affect the developing offspring in animals compared to humans. Adding to this conclusion is the lack of information on relevant human study populations and the lack of understanding of bromide's role in humans presenting with thyroid disorders.

2. Iodide- and chloride status in the human body and their impact on threshold for bromide thyroid toxicity

The chloride intake substantially affect the biological half-life of bromide (Czerwinski, 1958; Van Logten et al., 1974; Trump et al., 1976[2]), with an increase in bromide half-life of up to ten times with decreasing chloride uptake. The chloride status in the European population is not known (and has not been researched by the eCA), but considering that studies show that a salt-free diet can increase the biological half-life of bromide (Van Logten et al., 1974) it is reasonable to assume that the chloride status is relevant when setting a threshold for bromides endocrine effects, as the European population's intake of chloride varies substantially. The chloride status should therefore be considered in setting a threshold for bromide.

Similarly, the iodide intake affects the biological half-life of bromide (Buchberger et al., 1990[3]). Again, the iodine intake in the population varies, and it has been reported that up to 1/3 of the global population are iodine-deficient (Zbigniew, 2017), and iodine deficiency is a major health problem in Europe (Vitti et al., 2003; Delange, 2002). Some European countries have tried to account for the low intake by adding iodide to salt, bread, milk and other foods but problems are still present in these populations (Manousou et al., 2016). The iodine status should therefore be considered in setting a threshold for bromide's endocrine effects.

3. Evaluation of the endpoints in the submitted studies for use in setting a threshold for bromide thyroid toxicity

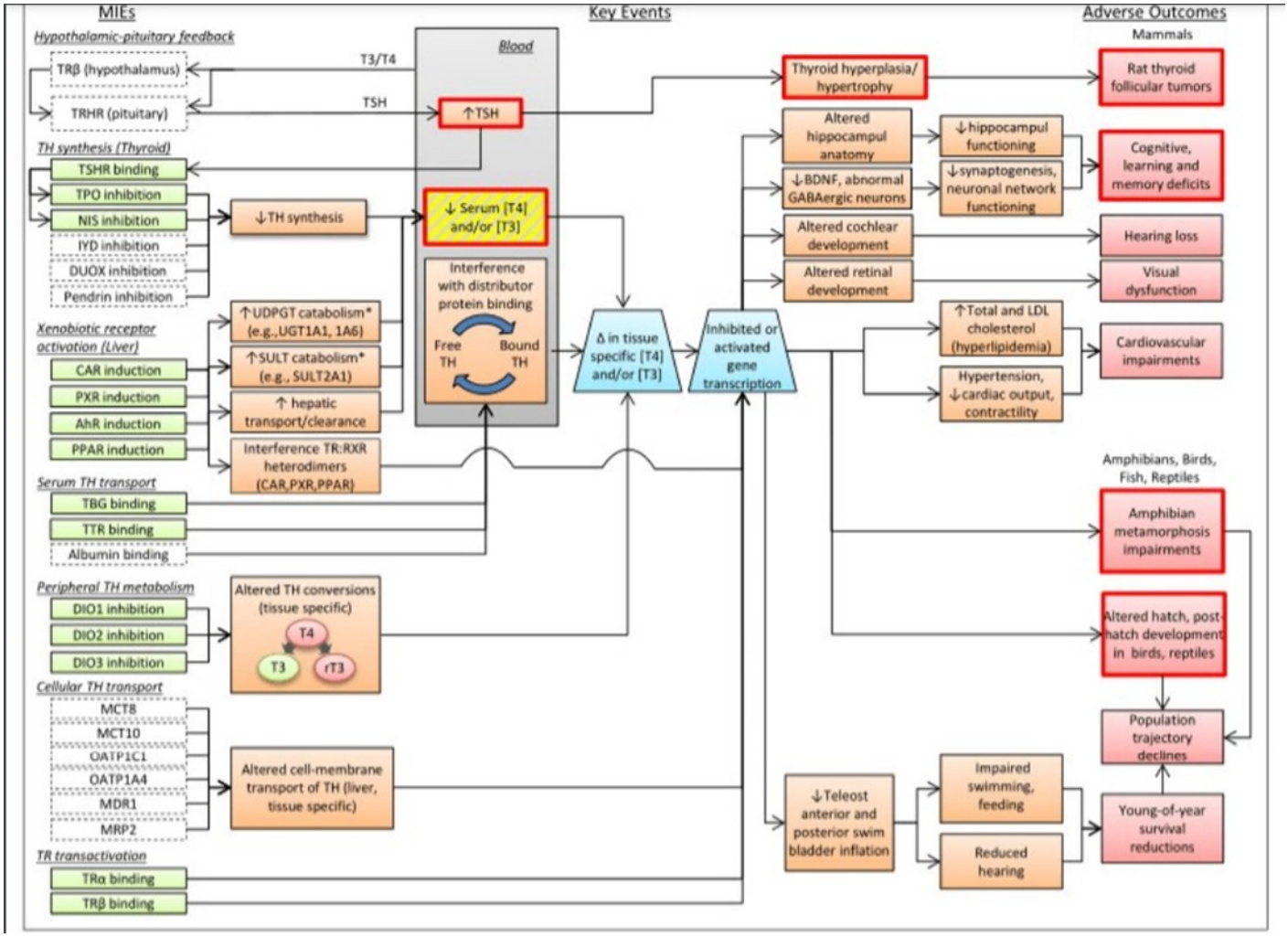
In order to evaluate whether or not the submitted information is relevant for setting a threshold, the relevance of effects for setting this threshold should be clearly defined. This calls for an evaluation of the Adverse Outcome Pathway (AOP) network following thyroid disruption. The AOP network for thyroid disruption is shown in figure 4.1-1. This AOP is not exhaustive of thyroid adverse effects, but the most researched adverse outcomes are included. Only these will be considered relevant for the risk assessment.

In the hazard assessment of the ED properties of bromide (in the DBNPA PT4 Assessment Report) all key events and adverse effects were considered. For the current assessment of risk from thyroid disruption, only adverse effects are considered relevant, as a threshold relates to threshold of toxicity/adverse effects, while the hazard assessment relates to the activity and potential for adversity. In the hazard assessment the evidence of thyroid hyperplasia acted as a surrogate for the adverse effects as depicted in figure 4.1-1 due to lack of data. This is legitimate considering that the two events are of course related. In order to set a threshold, one must however also know the degree (concentration of substance) to which this key event will lead to an adverse outcome and the level of severity of adverse effect. Below is listed the different adverse outcome relevant for the risk assessment in humans (therefore only the mammalian adverse outcomes, excluding the "rat thyroid follicular tumors" as this is only relevant for rats) and whether or not information submitted by the consortium is available for these.

Figure 4.1-1

[2] Not an exhaustive list of references. References was searched in PubMed using the search terms "bromide" AND "chloride". Titles and abstracts were screened, and the most relevant was included as use for reference. A systematic literature review was not conducted.

[3] Not an exhaustive list of references. References was searched in PubMed using the search terms "bromide" AND "iodine" OR "iodine". Titles and abstracts were screened, and the most relevant was included as use for reference. A systematic literature review was not conducted.



(As explained in above, possible inter-species deficiencies may exist, especially related to this point, however, this will not be addressed in this section)

a. Cognitive, learning and memory deficits

The most sensitive population for effects on learning abilities and memory is the developing individual, both when *in utero* and postnatal. Fully-developed mammalians may also be affected on these parameters, but only would they not represent the most sensitive population, the very evident cofounder of bromide's additional toxicity directly on the nervous system would also make it difficult to establish if the effects on mental state/learning ability/memory would be caused by a thyroid disruption or bromide's neurotoxic effects.

Only one of the submitted studies (Hamilton et al., 1944) investigated the learning ability (maze) of rat offspring when administered sodium bromide prenatally and through mother milk until weaning. Pups treated 80 and 120 mg/kg bw/day made significantly more errors, and the NOAEL for this endpoints was set at 40 mg/kg bw/day. A few studies investigated behavioural effects, but the specific endpoints investigated could also be attributed to bromide's sedative effects (response rates of rats). When using information on behavioural effects, it is recognized that a battery of tests is necessary due to large intra-species variations in performance within these studies. The eCA has therefore not considered the study by Hamilton et al. in the further risk assessment, as this was the only study available for evaluation of behavioural effects.

b. Hearing loss

Hearing loss is a sensitive marker of thyroid disruption, both in the adult population (e.g. sudden sensorineural hearing loss) (Zhu et al., 2020) as well as in the developing organism (Meza et al., 1996, Ng et al., 2009) as thyroid hormones are responsible for the development of the auditory system[4]. However, none of the submitted studies investigated this endpoint. No further assessment is possible.

c. Visual dysfunction

Acute visual dysfunction is usually correlated with hyperthyroidism. Bromide causes hypothyroidism, in which acute visual dysfunction is only correlated to swelling in the eye area (Weiler, 2017). Evidence however suggest, that hypothyroidism affect the contrast sensitivity in the development of the eye functions (Mirabella et al., 2005)[5]. However, none of the submitted studies investigated this endpoint, and therefore no further assessment is possible.

d. Cardiovascular impairments

The cardiovascular signs and symptoms of thyroid disease are some of the most profound and clinically relevant findings that accompany both hyperthyroidism and hypothyroidism. Thyroid hormone exacerbate changes in cardiac output, cardiac contractility, blood pressure, vascular resistance, and rhythm disturbances. Klein et al. (2016)[6] has described endpoints relevant for detection of cardiac impairment. However all of these endpoints are of acute onset with large intra-species variations as well as management variations and therefore difficult to interpret in animal studies when study focus is not directly on observation of these effects. As none of the submitted studies focus specifically on these endpoints, no further assessment is possible.

4. Subclinical hypothyroidism in humans and the relevance in setting a threshold of toxicity

When wanting to set a threshold of adverse effects for humans, it is in the eCA's opinion, that considerations of subclinical hypothyroidism should also be included due to its prevalence in the European population and the clinical effects following this. Thyroid hormones affect numerous mechanisms in the human body at which also subclinical hypothyroidism (thyroid hormone levels are within the normal range) e.g. causes cardiac impairment (Klein et al., 2007) leading to clinical adversity. As there are great intra-species variations in thyroid hormone levels, it is difficult to establish a common quantifiable threshold where no risk of thyroid disturbance can be ensured.

Overall conclusion for setting a threshold of adverse effects in humans from exposure to bromide

The eCA concludes that a quantifiable threshold for human adverse effects cannot be set based on the information available for bromide. Too many factors affect the true biological threshold for endocrine disruption at which exposure bromide will lead to adverse effects. To summarize, factors making it difficult to set a quantifiable threshold are:

1. Species-specific physiology difference in the thyroid hormone system makes it difficult to use animal studies to derive a threshold, as information on these differences are scarce.

2. The iodine and chloride status of humans vary within regions, and the internal levels of these halogens has been proven to affect the metabolism of bromide. Specifically, up to 1/3 of the global population are

[4] Not an exhaustive list of references. References was searched in PubMed using the search terms "hearing loss" OR "auditory development" AND "bromide". Titles and abstracts were screened, and the most relevant was included as use for reference. A systematic literature review was not conducted.

[5] Not an exhaustive list of references. References was searched in PubMed using the search terms "bromide" AND "visual development" OR "visual dysfunction". Titles and abstracts were screened, and the most relevant was included as use for reference. A systematic literature review was not conducted.

[6] Not an exhaustive list of references. References was searched in PubMed using the search terms "bromide" AND "cardiac impairment". Titles and abstracts were screened, and the most relevant was included as use for reference, in this case a review. A systematic literature review was not conducted.

experiencing iodide-deficiency, which decreases the threshold for bromide thyroid toxicity. The level of threshold for bromide is therefore not static, but depends on the iodide-/chloride status.

3. The submitted studies on bromide do not investigate the most sensitive endpoints relevant for establishing a NOAEL to potentially use as Point of Departure. Some considerations were made by the eCA to try and account for this missing information. For example, it could be argued, that apical endpoints could also be used in the risk assessment, as thyroid disturbance cannot lead to adverse effects if not disturbed (hence, if no effects on the key events of the AOP, then there should be no effect in adversity), but considering the many other factors affecting the uncertainties in setting a quantifiable threshold for bromide, use of this methodology has not been attempted by the eCA.

4. Similar to the population variations in internal levels of chloride and iodide, variations in clinical adversity from thyroid disruption exists, meaning that even subclinical hypothyroidism can lead to adverse effects in individuals, making the assessment of apical endpoints (like thyroid hormones) when trying to set a threshold for humans difficult.

4.2 Risks for humans – section 10(b) of the mandate

4.2.1 Acceptable daily intake – section 10(b)1

Bromide salts are not authorized for treatment of epilepsy in humans within Europe. The European Agency for the Evaluation of Medicinal Products (EMEA) referred to the use of potassium bromide as an anticonvulsant in humans at up to 6g/person/day (EMEA, 1997), but no potassium bromide human medicinal products have been or are approved within the European central system and, similarly, it seems that there is no nationally approved human potassium bromide medicines. European Medicines Agency (EMA) was contacted to assist in locating possible earlier assessments of this use considering the aforementioned reference to its use, but EMA does not hold any information or assessment on this active and/or its past use in human patients. Some references on its previous use as anticonvulsants in humans (Flinn et al. 1941; Levine, 2000; Kodama et al., 2019) and its current use in canine epilepsy have been available to the eCA. The studies on use in canine treatment of epilepsy were discarded as they are not relevant. The publications on the human use as anticonvulsant did not evaluate relevant adverse effects; only a few clinical effects related to clinical bromism was evaluated. The studies are therefore not suitable for use in this risk assessment.

EMA has currently only authorized products containing glycopyrronium bromide for use in maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) (CHMP 2012a; CHMP 2012b) and in the treatment of sialorrhoea (chronic pathological drooling) in children aged 2 to <18 years with neurological disorders (CHMP 2016). The different glycopyrronium bromide medicinal product reports only include endpoints which are either only relevant for the acute exposure and/or clinical adversity when chronically exposed. None of these endpoints are relevant for assessment of the potential for ED effects. Therefore, the use of these indicated treatment dosages as indication of a safe exposure to bromide is not appropriate when addressing bromide's ED properties.

EMA and WHO has derived acceptable daily intake (ADI) values, but for other areas of regulation:

Regulatory thresholds (ADI)

During a joint meeting of the Food and Agriculture Organization of the United Nations/WHO in 1988, an acceptable daily intake (ADI) of 0–1 mg/kg bw (body weight) was established for the bromide ion (FAO/WHO 1989), based on a NOEL of 9 mg Br^-/kg bw/day from a toxicological review by Van Leewen et al. (1987).

The European Agency for the Evaluation of Medicinal Products (EMEA, 1997) also utilized this review by Van Leewen et al. (1987) to derive an ADI of 0.4 mg/kg bw based on marginal effect within normal limits of electroencephalograms in female volunteers at 9 mg/kg bw per day, including a safety factor of 10 for population diversity.

Furthermore, several MRLs in various food groups have been established by the European Commission, but as they do not address the actual intake of bromide, they were discarded for use in this assessment.

Drinking water limits by the World Health Organisation (WHO)

The WHO Guidelines for Drinking-water Quality (GDWQ) did not establish a drinking water guideline for bromine as it quickly forms hypobromous acid and bromide in water. A drinking-water guideline value was,

however, not considered necessary for bromide as it occurs in drinking-water at concentrations well below those of health concern (WHO, 2017). However, should bromide be found in the drinking water or its sources, the WHO provided a health-based value of 6 mg/L for adults and 2 mg/L for children in the GDWQ for the Member States. These values were based on the ADI of 0.4 mg/kg bw/day (WHO, 2009 and 2018a).

All abovementioned ADIs from EMA and FAO/WHO and drinking water limits by WHO were established by assessment of both animal and human studies and with special emphasis on a review of the bromide ion performed by Van Leewen al. (1987). In this review a NOEL of 4 mg/kg bw/day was established based on effects in electroencephalogram (ECG) measurements in human adult volunteers at 9 mg/kg bw/day (LO(A)EL) (Sangster et al., 1983 and 1986). The Joint FAO/WHO Expert Committee on Food Additives (JEFCA) did not find these effects significant for use as Point of Departure (POD) and therefore in their assessment, the POD was based on the 9 mg/kg bw/day dose within this study considering that the ECG results were significant, but still within normal range. In deriving the ADIs a safety factor (SF) of 10 was applied by EMA, and FAO/WHO (1989) estimated an ADI in the range of 0-1 mg/kg bw/day (equivalent to a SF of 9).

In order to establish the appropriateness of the abovementioned ADIs for use in the risk of ED effects the eCA reviewed these studies with emphasis of their ability to detect thyroid disrupting effects.

Please refer to table 4.2.1-1 for the reference values.

The eCA considers that the studies used for derivation of the before mentioned ADIs are not sensitive enough for evaluating risk of ED effects, primarily due to the fact that they are performed on healthy adult human volunteers. The effects used as POD was interference in ECG by EMA, which are effects related to bromide's direct neurological impact. Two of the studies (Sangster et al., 1983 and 1986) included endpoints relevant for thyroid disruption (measurement of t4, t3 and TSH) where no significant effects were seen in the 1986 study, but an increase in t3 and t4 was seen at certain points in the study period in females in the 1983 study. Considering that this study was performed on healthy adult volunteers and that plasma levels of study population was relatively low compared to the average daily intake (as reviewed and assessed in section 4.2.3), the sensitivity could be questioned, as the sensitive human populations are developing fetuses (and pregnant females), children and possibly adolescents. Also, while sensitive endpoints do include changes in thyroid hormone levels, these are not the most sensitive. Furthermore, considering the lack of information related to the correlation of thyroid hormone levels in humans and the clinical effects in humans, further difficulties exist in the interpretation of these endpoints for use in a risk assessment. Additionally, a safety factor (SF) of 10 was added due to the study being performed on humans, and while this is the standard in regulatory risk assessment, it is difficult to assume that this SF takes into account the differences in sensitivity to the adverse endocrine effects of bromide between healthy adult volunteers to e.g. iodine-deficient, chloride-deficient and/or pregnant females and/or developing fetuses, as this has not been researched. These factors may be relevant in setting the level of threshold of toxicity for bromide (please refer to section 4.1 of this mandate for a discussion on these factors).

Although not directly requested by the mandate, other regulatory institutions besides WHO and EMA have set ADIs, these have included for completeness sake; Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT) (COT, 2000) set an ADI of 0-1 mg/kg bw/day based on the joint FAO/WHO assessment, Food safety commission of Japan and National Sanitation Foundation (NSF) set an ADI of 0.9 mg/kg bw/day based on the same studies as presented above and applied a SF of 10.

The eCA concludes that none of the above ADIs are relevant as safe reference values against the exposure to bromide from DBNPA in PT4 when establishing a safe level of risk from ED effects based on the conclusion that the studies used for the POD is not relevant for the risk assessment of bromide's endocrine properties and the SF may not take into account all relevant sensitive populations.

Table 4.2.1-1 Reference values currently used by international organizations

Organisation/year of evaluation	Substance	Usage area	Source of reference value for toxicity	Effect(s) from which reference value is based on	Reference value(s)

EMEA, 1999	Bromide, potassium salt	MRL for use as a hypnotic sedative in cattle, sheep, horses and pigs ADI	POD = 4 mg/kg bw/day from human studies with NaBr from 84 days human studies (Sangster 1983 & 1986, Van Gelderen 1993)	At 9 mg/ kg bw/day: Quantitative analysis of the EEG showed significant effects in the groups of volunteers taking 9 mg kg-1 bromide. These effects stayed within normal limits as well. Safety factor 10	ADI 0.4 mg/kg bw/day
EMEA, 1997	Bromide, sodium salt	MRL for topical use on all food producing animals ADI	POD = 4 mg/kg bw/day from human studies with NaBr from 84 days human studies (Sangster 1983 & 1986, Van Gelderen 1993)	At 9 mg/ kg bw/day: Quantitative analysis of the EEG showed significant effects in the groups of volunteers taking 9 mg kg-1 bromide. These effects stayed within normal limits as well. Safety factor 10	ADI 0.4 mg/kg bw/day
FAO/WHO, 1989	Bromine	ADI for total food intake of inorganic bromide from all sources	POD = 9 mg/kg bw/day from a 84 days human intervention study's (Sangster, 1983 and 1986) POD = 300 NaBr/kg diet (corresponding to 12 mg/ kg bw/day NaBr) from a 90day study in rats	ADI set on basis of minimally pharmacologically active dose of potassium bromide which was claimed to be generally stated to be about 900 mg/person/day (no reference) equivalent to approx. 600 mg Br'/person/day (10 mg Br/kg bw/day). At the joint FAO/WHO meeting in 1967. Reaffirmed in the Inorganic bromide was evaluated by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1966, which recommended an acceptable daily intake (ADI) for humans of 0–1 mg/kg body weight, based on a minimum pharmacologically effective dosage in humans of about 900 mg of potassium bromide, equivalent to 600	ADI 0-1.0 mg/kg bw/day

				mg of bromide ion. The JMPR ADI of 0–1 mg/kg body weight was reaffirmed with new data in 1988. Safety factor of 9.	
WHO, 2018a WHO, 2017	Bromide in drinking-water	ADI, drinking water	POD = 4 mg/kg bw/day from human studies with NaBr from 84 days human studies (Sangster 1983 & 1986, Van Gelderen 1993)	Based on the ADI of 0.4 mg/kg bw/day (referred to from EMA summary report) for a 60 kg adult consuming 2 L/day of water or 10 kg child consuming 1 L/day	6 mg/L for adults and 2 mg/L for children
COT, 2000	Bromine	ADI	Based on joint FAO/WHO assessment	The UK Committee on Toxicity (CoT) considered the dietary intake of bromine in 2003. The committee reviewed an evaluation by JECFA and JMPR that established an ADI of 0-1 mg/kg body weight. COT considered it inappropriate to recommend a range of intakes for bromine that included zero, as it is not certain that bromine is essential. They considered the upper boundary of 1 mg/kg body weight as an intake below which intakes are unlikely to pose a risk to health.	ADI 0-1.0 mg/kg bw/day
FSCJ, 2015	aqueous solution of hypobromous acid (food additives).	ADI	POD = 9 mg/kg bw/day from a 84 days human intervention study (Study reference not specified; appears to be based on Van Gelderen, 1993)	No significant effects seen in a 84 day study in human volunteers	ADI 0.9 mg/kg bw
US EPA, 2010	Bromine	RfD ADTC chronic	POD = NOAEL of 20 mg/kg/day, based on a 28-day study in rats with ethanolammonium perbromide	Salivation and decreased activity, increased PCV, RBC and haemoglobin values reversible in 14 days	ADTC chronic RfD = 0.2 mg/kg bw/day

NSF, 2011	Bromine/bromide	RfD	Pod: 9 mg/kg bw/day, adjusted bromide 7 mg/kg bw/day (Van Gelderen et al. (1993) and Sangster et al. (1983) studies) TAC (total allowable concentration): 10 mg/L (total concentration of bromine and bromide) For a 70 kg adult drinking 2 L/day using a 50% relative source contribution for drinking wate	Absence of sedation and EEG changes within normal limits	Oral RfD 0.7 mg/kg bw/day 10 mg/L drinking water

4.2.2. Essential for human life – section 10(b)2

From 2014, bromide has been recognized as being essential for animal life after McCall et al. (2014) presented evidence of bromide being essential for the assembling of collagen IV scaffolds in tissue development and architecture in Drosophelia. Specifically, Br− is a required cofactor for peroxidasin-catalyzed formation of sulfilimine crosslinks, a post-translational modification essential for tissue development and architecture found within the collagen IV scaffold of basement membranes. Bromide, converted to hypobromous acid, forms a bromosulfonium-ion intermediate that energetically selects for sulfilimine formation. Additionally, a study in goats (Ceko et al. 2015) compared goats fed bromine-deficient diets to goats with a standard diet, where growth and fertility was depressed in the bromine-deficients goats. Also, in a study on chicks receiving Cl- deficient diets, it was found that dietary supplementation (676–1352 mg/kg) of bromine counteracted most of the symptoms of Cl- deficiency in chicks fed a Cl- deficient diet. The different key findings are presented in table 4.2.2-1.

Although evidence for bromide's function in animal tissue has only been recognized from 2014, several earlier studies (Cross et al. 1981; Cuenca et al. 1988; Alexiou et al. 1977) have investigated the bromine content (and analysed the bromide part) in human and animal tissues -owing to a general understanding of its essentiality before 2014 considering its natural presence in the human body. Studies of serum/plasma/whole-blood levels is included in table 4.2.2-2 to present normal ranges in the human body in a simple way. Several studies on the distribution of bromide in tissues within the human body also exists. These are not presented in the table in order to focus on values for comparison. As can be seen, the presented mean values of human serum/whole blood levels are consistent across studies, as well as indication of external exposure to bromide leads to significant changes of interval levels of bromide (Nusair et al., 2019). One study (Allain et al., 1993) also compared the internal level of bromide with changes in thyroid hormones. This study concluded that bromine concentrations above 6 mg/L (0.08 mmol/L) were considered above the normal range, but changes in thyroid hormone levels were observed at bromide plasma concentration above 13 mg/L.

Evidence clearly suggest that bromide is an essential trace element for human life and development, and that interval bromide levels are within a defined range. It is however not possible to determine the *minimum* internal levels of bromide essential for human life based on the submitted studies.

Table 4.2.2-1 Studies on essentiality for bromide in the human body

Study reference	**Species**	**Key findings**	**Key conclusions**

McCall et al., 2014	Drosophila	Bromine dietary deficiency is lethal in Drosophila, whereas bromine restores viability - Br- is required for sulfilimine formation within collagen IV, an event critical for BM assembly and tissue development	Br- required for sulfilimine formation within collagen
Ceko et al., 2015	Chick	By the end of this 14-year period, only weak evidence existed to support the view that bromine is essential, with one of the key findings being that bromide (Br-) can substitute for part of the chloride (Cl-) requirement for chicks. In particular, dietary supplementation (676–1352 mg kg-1) counteracted most of the symptoms of Cl- deficiency in chicks fed a Cl- deficient diet.	-Dietary supplementation of Br- at 676–1352 mg/kg bw counteracted symptoms of Cl- deficiency in chicks
Ceko et al., 2015	Goat	In 1990, one additional study reported that, when compared to goats fed 20 mg bromine per kg diet, goats fed a 0.8 mg bromine per kg diet exhibited depressed growth, fertility, reduced life expectancy and more abortions	Deficiency of bromine depressed growth, fertility, reduced life expectancy in goats

Table 4.2.2-2 References, measured levels of bromide in human tissue/blood

Study reference	**Key findings**	**Mean normal values**
Olszowy et al., 1998	Aged persons (45-65+ years) are more likely to have higher bromide levels than younger persons (15-25 years). Average levels were higher in females in most age groups. No significant differences in bromide levels were found in persons living in the highly populated southeast region of Queensland compared with those living in the less urbanized northern parts of the state.	**5.3 +/- 1.4 mg/L and ranged from 2.5 to 11.7 mg/L whole blood**
Nusair et al., 2019	Cross sectional study in humans: Normal Br- levels in human serum was reported with a mean value of 3.9 mg/L -Previous reports indicated that the average Br^- burden in exposed populations was 15.33 –17.7 mg/L compared to 4.1 and 8.69 mg/L in non-exposed populations - Average serum Br- in Ghor As-safi (Jordan valley) (16.35 mg/L) was higher than the normal value - People in Deir Alla (Jordan) had higher average serum Br^- (8.01 mg/L) than the normal level - 19 out-door workmen at Dead sea area had higher average Br- (11.9 mg/L) levels	Normal Br- levels in humans**: 3.9 mg/L (mean) serum** - Br- levels due to anthropogenic exposures (bromine factory) in humans: **15.33 –17.7 mg/L**
Van Leeuwen et al., 1987	Bromide concentration (mg/kg) in human blood Subjects No. Mean ± SD Range Healthy adults 5 3.9 ± 2 2.0 a - Healthy adults 16 3.9a 1.6-12.6 Females 38 4.0 ± 0.8a 2.6-5.9 Females 38 5.1 ± 0.5b 3.4-7.5	-Mean bromide levels ranging from **3.5 to 4.9 mg/kg whole blood**, and slightly higher plasma level in humans.

	Males 35 3.5 ± 0.7a 2.6-5.4 Males 35 5.1 ± 0.9b 4.0-7.3 Healthy adults 163 4.6 ± 0.8a - Draftees 1275 4.9 ±1.6a 0.2-15.8 Females 21 5.4 ± 1.0b - Males 21 5.8 ± 0.8b - a= Whole blood. b= Blood plasma	
Eldan et al., 1996	Bromine occupational exposure levels: - The average level found in the study population was 22.9 ppm, with a minimum of 8.3 ppm and a maximum of 428.6 ppm -The range of serum Br- in the general population is 3 to 5 ppm -Toxic levels are defined as SeBr above 700 ppm	Serum bromine levels in general population between **3 and 5 ppm**
Allain et al., 1993	799 patients examined for thyroid disorders. Comparison of normal subjects against thyroid affected patients. Bromine levels in adults with thyroid disorders -Bromine plasma concentration in normal' subjects = 4.1 ± 0.9 mg/L (0.051 mmol/L) - Bromine concentrations above 6 mg/L (0.08 mmol/L) were considered above the normal range -Mean plasma bromine concentration in patients with normal TSH and T4 levels was 13 mg/L (0.16 mmol/L), compared to 38 mg/L (0.48 mmol/L) in patients with high TSH, but normal T4 levels	Bromine plasma concentration in normal' subjects = **4.1 ± 0.9 mg/L (0.051 mmol/L)** Bromine concentrations **above 6 mg/L (0.08 mmol/L**) were considered above the normal range

4.2.3 Contribution of DBNPA-derived bromide – section 10(b)3

Several market basket surveys and total diet studies have been published on the average daily bromide intake in humans. The available studies are presented in table 4.2.3-1. Although differences between the methods of the different studies exist, results are relatively consistent across studies concerning the average bromide ion dietary intake. Correlating the different study periods and mean daily bromide intake, a decrease in dietary bromide intake is seemingly apparent: De Vos et al. (1984) and Van Dokkum et al. (1989) performed similar studies within the same study population and a decrease in bromide intake was found; from 9.4 mg Br/person/day in 1976-78 to 8 mg Br/kg bw/day in 1984-86. Miller et al. (2001) performed a total diet study of the UK population in 1997, and a daily intake of bromide was 3.6 mg/person/day. This is in contrast to the UK total diet study (UK, 1981) of 1978 and 1979, where a daily intake was 8.4 mg/person/day in the UK. One of the explanations could be that the earliest diet studies were conducted at a time where the use of potassium bromate in bread making was not yet prohibited in Europe, as it is now. This was noted in one study (van Dokkum et al., 1989), that the two sampling periods between 1976 and 1978 resulted in significant difference (from 12.7 mg/kg to 4.2 mg/kg) in bromide residues within the same food group (cereal products) which was argued to be caused by the prohibition of potassium bromate. JEFCA concluded in its 39th meeting (1992) that potassium bromate was not appropriate for use as a flour treatment agent due to its possible carcinogenic properties (JEFCA 1992). In its 44th meeting the conclusion was reaffirmed (JEFCA 1995). Van Dokkum et al. (1989) argued that potassium bromate was prohibited in the study area during the study period. It was not possible to locate official information related to this.
Similarly, and relevant for all studies, all results from the dietary studies may be overestimates of today's bromide intake given the fact that no studies have been performed where methyl bromide was not withdrawn for use as a pesticide. Methyl bromide was prohibited for use as a pesticide in 2009 (2008/753/EC COMMISSION DECISION). Considering the fact that studies[7] (Cova et al. 1986; Huang et al. 2005; Scheffrahn et al. 1992; Dumas et al. 1973; Dimitriou et al. 1998) show that the use of methyl

[7] Studies was found by the eCA by search terms "methyl bromide" AND "residue*" in PubMed. Titles and abstracts were screened, but no reliability assessment was performed, and only abstract were reviewed.

bromide can increase bromide residues levels in crops substantially, this confounder has specifically been discussed and addressed in some of the diet studies.

Considering the decline seen over the years in dietary bromide intake, the most relevant daily intake value from the published research studies to use as reference against the possible exposure to DBNPA-derived bromide is from the 1997 UK Total Diet Study (Rose et al., 2001). Although not knowing to which degree methyl bromide was being used at this time in UK and therefore its impact on the UK daily dietary intake of bromide, it should be noted that methyl bromide was only used as a pesticide for certain food groups, and the 1997 UK total diet study was composed of the typical total diet and not only food from possible methyl bromide treated food items. The potential increase in bromide residue in some food groups due to the use of methyl bromide should not discard the use of the derived average daily intake from this study as the obtained daily intake values of bromide are derived from a total diet, and thus the use of methyl bromide should not distort the obtained daily intake values to a level of concern.

Table 4.2.3-1 References human diet studies on average daily intake of bromide

Reference	Study period	Study description	Key findings	Average daily intake
Van Dokkum et al., 1989	1984-1986	Market basket survey. Total diet study for 18 year old Dutch males over a period of 2.5 years.221 food groups.	Discussion concerning the high food intake of 18 year old males, emphasizing the daily intake as being representative of other age groups.	8 mg/person/day 0.13 mg/kg bw/day[2]
UK, 1981 (unpublished)	1978 and 1979	Total diet survey UK population.	Details of study found in joint FAO/WHO evaluation 1981. No access to original study	8.4 mg/person/day 0.14 mg/kg bw/day[2]
Cross et al., 1978	1978	Total diet study for one week of a typical diet in Glasgow.	Values were also compared to human tissue levels of bromine. The paper discusses the addition of potassium bromide to bread making to assess the level of contribution and risk.	9 mg/kg bw 0.15 mg/kg bw/day[2]
De Vos et al., 1984	June 1976-july 1978	Market basket survey. Holland Healthy 18-year old men, average daily intake items Total bromine over two years, sample every two months, 2 week period intake (in total 12 samples), 126 food items.	Highest content in grains, cereals and oils and fats composites, The oils and fats composite contained, among others, peanut butter and peanut sauce, which may have been prepared from fumigated peanuts. The higher bromine levels in the grain composite may also be caused by the use of potassium bromate as an improver in the breadmaking process during which the bromate is converted into bromide.	9.4 mg/person/day 0.156 mg/kg bw/day[2]
Parr et al., 1992	1970-1991	Global literature survey. Data submitted to IAEA in response to questionnaire	Database compilation on human dietary intakes of trace elements.	2.3-6.8 mg/day 0.0383-0.113 mg/kg bw/day[2]

		and publications from open scientific literature		
Rose et al., 2001	1997	Samples for the 20 Total Diet Study (TDS) food groups were obtained from 20 towns in the UK in 1997 and analysed in 1998/99 for total bromine and total iodine concentrations.	The highest average bromine concentrations were found in the Nuts group (25.8 mg/kg), the Fish group (6.7 mg/kg) and the Offals group (0.55 mg/kg) The Beverage group had the lowest average bromine concentration (0.1 mg/kg) The average population exposure to bromine was 3.6 mg/ day with the main contributors being Milk (22 per cent), Bread (14 per cent) and Miscellaneous cereals (11 per cent).	3.6 mg/day 0.06 mg/kg bw/day
Nielsen et al., 2009	Unknown	Dietary intake natural sources U.S.	Referenced for daily intake by WHO (2009).	2- 8 mg/day[8]
Greve et al., 1983	Summer 1976, winter 1978	24h sample total diet of 100 workers diet at National Institute of Public Health	The average daily intake found was 7.8 mg/person in the first study and 7.6 mg/person in the second study (with ranges of 2.9 15.0 and 1.8-17.2 mg/person/day, respectively). National surveys, covering several thousands of samples, showed that certain leafy vegetables and some herbs could occasionally contain high residues of bromide ion (> 200 mg/kg). **An important source of these high residues is the treatment of soils with methyl bromide** against nematodes.	7.8 mg/person/day 7.6 mg/person/day

However, in search of more recent data relevant dietary bromide intake reference values, the eCA consulted the annual European Union reports on food consumption. Regulation (EC) No 396/2005, Article 32, requests EFSA to conduct an analysis on the health risks to European consumers and publish this within an annual report on pesticide residues. These have been published by EFSA from 2007-2019.

The analysis from these reports are based on the results from official controls provided by reporting countries. The objectives, design of the national control programs, sampling method, analytical methods and key findings from each national control program is published in a separate report by EFSA. The analysis of the risk to health posed by the finding of residues is aided by the assessment of data on food

[8] Only abstract is available. Study has been withdrawn from the Journal from which it was published in. It is however included for purpose of transparency, but is not used in the risk assessment.

consumption by EFSA. The latest publically available report is the 'The 2019 European Union report on pesticide residues in food' and the supportive data from the national control programs is '2019 National Summary Report on pesticide residues'.

The 2019 report (and the previous reports) summarizes the results of both EU-coordinated control program (EUCP) and the national control programs. In the EUCP, bromide was predefined to be measured in lettuce and tomatoes in 2019 (and 2016 in a three year cycle monitoring program). In contrast, the national program samplings for bromide are risk-based in accordance with article 30 of Regulation (EC) No 396/2005. The priorities of the national control programmes are multifactorial, and includes both likelihood of finding residues in the foods, laboratory capacities and national diets.

In calculating the chronic exposure to bromide, EFSA used three approaches for chronic exposure assessment in the 2019 report: the lower bound scenario, the middle bound scenario and the adjusted upper bound scenario. From 2014-2018 they used a lower and upper bound approach. The different scenarios are used by EFSA to frame the boundaries of a realistic exposure estimate to pesticide residues. The use of limit of detection (LOD) to refine the adjusted middle or upper bound is not used by reporting countries as they do not systematically report these levels. The aim of the different scenarios is to better address the uncertainties linked to the presence of residues at levels below the level of quantification (LOQ).

a. The lower bound scenario assumes that samples with non-quantified residues (i.e. samples with residue levels < LOQ) are treated as if the residues are not present in the food product analysed. This scenario may result in an underestimation of chronic exposure.

b. The adjusted middle bound scenario assumes that samples with non-quantified residues (i.e. samples with residue levels < LOQ) are present in the sample at level of half of the LOQ.

c. The adjusted upper bound scenario assumes that samples with non-quantified residues (i.e. samples with residue levels < LOQ) are present in the sample at the level of LOQ. This scenario is the most overestimated.

Within the annual published reports, the average intake was considered by EFSA. The total dietary exposure for the different consumer groups in EU is also contained in annex III of the report. Table 4.2.3-1 presents the presented chronic intake of bromide from 2010-2019. The annual reports from 2006-2009 also include some information on bromide, however not in the format which could be relevant for use in this assessment. The values were presented differently in the different reports, but have been recalculated by the eCA in order to present comparable intakes.

Table 4.2.3-1 2010-2019 Annual reported chronic dietary exposure from the EU European Union report on pesticide residues in food.

Year	**Chronic exposure (in mg/kg bw per day)**		
	Lower bound approach	**Middle bound approach**	**Upper bound approach**
2019	0.012	0.075	0.145
2018	0.016		0.094
2017	0.0093		0.083
2016	0.0011		0.0087
2015	0.006		0.018

2014	0.0057		0.0122
2013			0.0649
2012			0.0442
2011			0.0537
2010			0.0541

As it was not possible to include chronic exposure calculations from the time period where the pesticide methyl bromide was still legally authorized, no comparison between these years against the years after where the use has been prohibited is possible.

However, an overview of the chronic bromide dietary consumption the years following the prohibition of the pesticide can be seen in table 4.2.3-1. As can be seen there is no clear decrease in human dietary intake of bromide. Considering that methyl bromide has been prohibited for use since 2005/2009 (depending on use area), this pesticide use should not cause overestimations of the presented annual dietary intake. However, some uncertainties still exist, which EFSA clearly has pointed out in the reports and which are mentioned above, but will shortly be summarized here: Although bromide residue levels have been measured, these have only been measured systematically in the EUCP in a small group of foods, and these vary from year to year (at the moment in three year programs), in 2016/2019 it was in tomatoes and lettuce, while in 2018 it was in rice for example. These are compared over a three year program to monitor the tendency. The national programs measure the bromide residues based on the individual EU member state's capacity and own national legislation and is not systematized, but can vary depending on several factors. Furthermore, although attempting to account for the fact that the different EU member states do not report the LOD for bromide, EFSA performs both upper, lower and middle based approaches concerning the use of the LOQ. However, the different results from these approaches yield exposure estimations that in several of the years varies with a factor of over 10 between the lower and the upper bound approach as bromide content in the majority of the samples is below the LOQ. Furthermore, the aim of the annual EU reports is to present the highest consumptions (as this is worst case in terms of residue level), while for this mandate, the aim is to derive the lowest consumptions. A simple way to overcome this would be to use the exposure from the lower bound approach, but this may be an unrealistic assumption due to the uncertainties stated above and would be an underestimation. As a result, the eCA has decided to present all reference values from the different approaches. The eCA has also decided to present all annual results to generate evidence of the bromide dietary intake throughout the years from 2010 to have a representation of the tendency of the bromide dietary intake, although they have not been generated in a systematically way. This could however aid in evaluating the overall tendency of bromide dietary intake in the most recent years.

In support of the overview in tendency for bromide residue levels in food, bromide ion residues was measured in lettuce and tomatoes in 2016 and in 2019 in the EUCP as previously explained. EFSA compared the percentages of samples with quantified residues between the two years. For lettuce, 27.37 % of the samples had residue levels between the LOQ and the MRL in 2019 where in 2016 23.72 % of the samples had residue levels between the LOQ and the MRL[9]. The same comparison was performed for tomatoes, at where 26.65 % of the samples in 2019 contained residue levels of bromide ion between the LOQ and the MRL in contrast to 31.18 % of the samples in tomatoes from 2016[10]. No samples in either of the years contained residue levels above the MRL. From this information, it can be seen that there is no clear decrease in bromide residue levels in the limited systematically sampled data for the two crops.

Although not requested, also studies on inhalation exposure to bromide was submitted to the eCA. This could be compared with the inhalation exposure from the primary use of DBNPA in PT4. However, the

[9] https://www.efsa.europa.eu/en/microstrategy/annual-pesticides-report-2019-lettuce
[10] https://www.efsa.europa.eu/en/microstrategy/annual-pesticides-report-2019-tomatoes

studies were not relevant for use as reference values as they were performed on workers working with bromide, and the effects measured did not included endocrine sensitive endpoints.

In conclusion, the eCA is of the opinion that the most appropriate reference values to use to compare the potential daily contribution of DBNPA-derived bromide from the use of the PT4 representative product against the normal daily consumption of bromide should be the mean value of 0.06 mg Br-/kg bw/day obtained from the 1997 UK Total Diet Study by Rose et al. (2001) from the published research studies and the lower, middle and upper bound average daily intakes reported in the 2019 European Union report on pesticide residues in food. It should be emphasized that these reference values are not considered as safe exposure levels of bromide intake. No assessment of these exposure levels' impact on human health has been performed. They are used to compare the exposure of bromide from use of DBNPA in PT4. The question on whether or not the exposure from dietary intake is within a safe level is outside the scope of this mandate.

Only the contribution of the use of PT4 should be assessed and thus the contribution via other PTs is not considered.

As concluded above, the most relevant reference value to compare the exposure from PT4 DBNPA-derived bromide is the average daily intake from the UK Total diet study of 1997 (Rose et al. 2001) of 0.06 mg/kg bw/day and the lower, middle and upper bound average daily intake from the 2019 European Union report on pesticide residues in food (lower: 0.012 mg/kg bw/day, middle: 0.075 mg/kg bw/day and upper: 0.145 mg/kg bw/day). When comparing these reference values against the bromide intake from use of DBNPA in PT4, it must be emphasized that the average daily intake is not used as toxicological reference/threshold of toxicity in this assessment. The use of these reference value is to compare the exposure to bromide from the representative use of DBNPA in PT4 to the already daily intake from other sources, as is requested in the mandate.

Table 4.2.3-3 presents the exposure of DBNPA in PT4 from the intended uses of the reference product which has been transferred directly from the agreed CAR DocIIC. Table 4.2.3-4 presents the amount of bromide exposed to from use of DBNPA in product type 4 from the intended uses of the reference product from the UK Total Diet Study. Similarly, table 4.2.3-5, 4.2.3-6 and 4.2.3-7 presents the amount of bromide exposed to from use of DBNPA in product type 4 against the lower, middle and adjusted upper bound approached exposure from the 2019 European Union report on pesticide residues in food.

Table 4.2.3-8 presents the indirect exposure of DBNPA to the general public related to the intended uses. Table 4.2.3-9 presents the amount of bromide, the general public is exposed to indirectly against the UK Total Diet Study. Table 4.2.3-10, 4.2.3-11 and 4.2.3-12 presents the amount of bromide, the general public is exposed to indirectly against the lower, middle and adjusted upper bound approached exposure from the 2019 European Union report on pesticide residues in food.

The bromide exposure from the representative use of DBNPA in PT4 was calculated as: Molecular weight DBNPA: 241 g/mol, molecular weight of bromide: 79.904 g/mol = $Exposure_{bromide}$ [DBNPA] * (79.904*2) g/mol / 241 g/mol.

Table 4.2.3-3 Primary systemic exposure of industrial users against DBNPA dossier derived AEL

Exposure scenario Intended use	**PPE**	**Concentration [% DBNPA]**	**Exposure**			**% AEL [AELmedium term = 0.059 mg/kg bw/day]**	**Margin of safety (MOS)**
			Inhalation	**Dermal**	**Total**		
			[mg/kg bw/day]		**[mg/kg bw/day]**		
Application phase: Disinfection of food vessels/machinery disinfection (Automated mixing)	Tier 1: None	20	0.0153	0.0077	0.0229	39	260
	Tier 2: PPE RPE	20	0.0038	0.00077	0.0046	7.8	1280

Table 4.2.3-4 Primary systemic exposure of industrial users against UK 1997 Total diet study ADI

Exposure scenario Intended use	**PPE**	**Concentration [% DBNPA]**	**Exposure$_{bromide}$**			**Average Daily Intake (Rose et al. 2001) mg/kg bw/day**	**% ADI**
			Inhalation	**Dermal**	**Total**		
			[mg/kg bw/day]		**[mg/kg bw/day]**		
Application phase: Disinfection of food vessels/machinery disinfection (Automated mixing)	Tier 1: None	20	0.00507	0.00255	0.015	0.06	25
	Tier 2: PPE RPE	20	0.00126	0.000255	0.00303	0.06	5.1

Table 4.2.3-5 Primary systemic exposure of industrial users against EFSA 2019 report lower bound approached ADI

Exposure scenario Intended use	**PPE**	**Concentration [% DBNPA]**	**Exposure$_{bromide}$**			**Average Daily Intake Lower Bound 2019 mg/kg bw/day**	**% ADI LB**
			Inhalation	**Dermal**	**Total**		
			[mg/kg bw/day]		**[mg/kg bw/day]**		

Application phase: Disinfection of food vessels/machinery disinfection (Automated mixing)	Tier 1: None	20	0.00507	0.00255	0.015	0.012	125
	Tier 2: PPE RPE	20	0.00126	0.000255	0.00303	0.012	25.3

Table 4.2.3-6 Primary systemic exposure of industrial users against EFSA 2019 report middle bound approached ADI

Exposure scenario Intended use	**PPE**	**Concentration [% DBNPA]**	**Exposure$_{bromide}$**			**Average Daily Intake Midde Bound mg/kg bw/day**	**% ADI MB**
			Inhalation	**Dermal**	**Total**		
			[mg/kg bw/day]		**[mg/kg bw/day]**		
Application phase: Disinfection of food vessels/machinery disinfection (Automated mixing)	Tier 1: None	20	0.00507	0.00255	0.015	0.075	20
	Tier 2: PPE RPE	20	0.00126	0.000255	0.00303	0.075	4

Table 4.2.3-7 Primary systemic exposure of industrial users against EFSA 2019 report adjusted upper bound approached ADI

Exposure scenario Intended use	**PPE**	**Concentration [% DBNPA]**	**Exposure$_{bromide}$**			**Average Daily Intake Upper Bound mg/kg bw/day**	**% ADI UB**
			Inhalation	**Dermal**	**Total**		
			[mg/kg bw/day]		**[mg/kg bw/day]**		
Application phase: Disinfection of food vessels/machinery disinfection (Automated mixing)	Tier 1: None	20	0.00507	0.00255	0.015	0.145	10.3
	Tier 2: PPE RPE	20	0.00126	0.000255	0.00303	0.145	2.1

Table 4.2.3-8 Secondary exposure of consumers against DBNPA dossier derived AEL

Exposure scenario Intended use	PPE	Concentration [% DBNPA]	Exposure			% ADI* [ADI = 0.014 mg/kg bw/day]	Margin of safety (MOS)
			Inhalation	Oral	Total		
			[mg/kg bw/day]		[mg/kg bw/day]		
Exposure via food (infant drinks beverage from disinfected bottle, 5 kg)	-	1.5 %	n.r.	0.0012	0.0012	8.6%	1166
Exposure via food (toddler drinks beverage from disinfected bottle, 10 kg)	-	1.5 %	n.r.	0.000778	0.000778	5.6%	1799
Exposure via food (adult drinks beverage from disinfected bottle, 60 kg)	-	1.5 %	n.r.	0.000259	0.000259	1.8%	5401

Table 4.2.3-9 Secondary exposure of consumers against UK 1997 Total diet study ADI

Exposure scenario Intended use	PPE	Concentration [% DBNPA]	$Exposure_{bromide}$			Average Daily Intake (Rose et al. 2001) mg/kg bw/day	% ADI
			Inhalation	Oral	Total		
			[mg/kg bw/day]		[mg/kg bw/day]		
Exposure via food (infant drinks beverage from disinfected bottle, 5 kg)	-	1.5 %	n.r.	0.000796	0.000796	0.06	1.33
Exposure via food (toddler drinks beverage from disinfected bottle, 10 kg)	-	1.5 %	n.r.	0.000516	0.000516	0.06	0.86
Exposure via food (adult drinks beverage from disinfected bottle, 60 kg)	-	1.5 %	n.r.	0.0000178	0.0000178	0.06	0.03

Table 4.2.3-10 Secondary exposure of consumers EFSA 2019 report lower bound approached ADI

Exposure scenario Intended use	PPE	Concentration [% DBNPA]	Exposure$_{bromide}$			Average Daily Intake Lower Bound mg/kg bw/day	% ADI LB
			Inhalation	Oral	Total		
			[mg/kg bw/day]		[mg/kg bw/day]		
Exposure via food (infant drinks beverage from disinfected bottle, 5 kg)	-	1.5 %	n.r.	0.000796	0.000796	0.012	6.6
Exposure via food (toddler drinks beverage from disinfected bottle, 10 kg)	-	1.5 %	n.r.	0.000516	0.000516	0.012	4.3
Exposure via food (adult drinks beverage from disinfected bottle, 60 kg)	-	1.5 %	n.r.	0.0000178	0.0000178	0.012	0.2

Table 4.2.3-11 Secondary exposure of consumers EFSA 2019 report middle bound approached ADI

Exposure scenario Intended use	PPE	Concentration [% DBNPA]	Exposure$_{bromide}$			Average Daily Intake Midde Bound mg/kg bw/day	% ADI MB
			Inhalation	Oral	Total		
			[mg/kg bw/day]		[mg/kg bw/day]		
Exposure via food (infant drinks beverage from disinfected bottle, 5 kg)	-	1.5 %	n.r.	0.000796	0.000796	0.075	1.1
Exposure via food (toddler drinks beverage from disinfected bottle, 10 kg)	-	1.5 %	n.r.	0.000516	0.000516	0.075	0.7
Exposure via food (adult drinks beverage from disinfected bottle, 60 kg)	-	1.5 %	n.r.	0.0000178	0.0000178	0.075	0.02

Table 4.2.3-12 Secondary exposure of consumers EFSA 2019 report adjusted upper bound approached ADI

Exposure scenario Intended use	PPE	Concentration [% DBNPA]	Exposure$_{bromide}$			Average Daily Intake Upper Bound mg/kg bw/day	% ADI UB
			Inhalation	Oral	Total		
			[mg/kg bw/day]		[mg/kg bw/day]		
Exposure via food (infant drinks beverage from disinfected bottle, 5 kg)	-	1.5 %	n.r.	0.000796	0.000796	0.145	0.6
Exposure via food (toddler drinks beverage from disinfected bottle, 10 kg)	-	1.5 %	n.r.	0.000516	0.000516	0.145	0.4
Exposure via food (adult drinks beverage from disinfected bottle, 60 kg)	-	1.5 %	n.r.	0.0000178	0.0000178	0.145	0.01

As shown in the above tables, the exposure to bromide from use of DBNPA in PT4 is low compared to both the reference values from the UK 1997 Total Diet study and the reference values from the 2019 European Union report on pesticide residues in food when using the middle and adjusted upper bound approached reference values. Additionally, when reviewing the CAR (docIIB), it is stated that for the industrial user, only automated transfer of the reference product into closed systems are relevant for exposure estimation, and that the use of the input value for dermal and inhalation exposure is a worst case assumption, as it would otherwise be considered negligible. Especially for the inhalation exposure, DBNPA is not readily volatile and is not usually recommended to estimate for this work task. Furthermore, for the indirectly exposure via food (bottles), it should be emphasized that the bottles are also rinsed after disinfection, making the estimated exposure to bromide via these bottles clearly worst-case. The scenario was originally included in the DBNPA CAR for PT4 as no measurements of the actual residues within the bottles was available, but it is clearly stated in the original assessment that this exposure is highly unrealistic. Furthermore, as stated in the DBNPA PT4 BPC Opinion, more data are expected to be submitted in order to demonstrate the relevance and effectiveness of this rinsing step at the product authorisation stage.

In conclusion, exposure from PT4 DBNPA-derived bromide further contributes to the average daily dietary exposure of the general population by 0.03-1.33 % and the primary user by 5.1 % if considering the normal average daily intake from the UK 1997 Total Diet Study. If considering the values presented in the 2019 European Union report on pesticide residues in food, exposure from PT4 DBNPA-derived bromide contributes to the average daily dietary exposure of the general population by 0.2-6.6 % and the primary user by 25 % considering the lower bound average daily dietary exposure, of the general population by 0.02-1.1 % and the primary user by 4 % considering the middle bound average daily dietary exposure and of the general population by 0.01-0.6 % and the primary user by 2.1 % considering the upper bound average daily dietary exposure.

4.2.4 Assessing level of risks – section 10(b)4

In the assessment of the level of risk for endocrine disruptive effects in humans following use of DBNPA in PT4, a semi-quantitative risk assessment has been performed.

The quantitative part of this assessment consists of evaluating the contribution of PT4 DBNPA-derived bromide against the dietary exposure to bromide. The qualitative part consists of evaluating the conclusions of the recitals of the mandate in a joined assessment.

The conclusions on the risk from ED properties related to human health were:

a) A threshold exists for the endocrine disruptive effects of bromide. It is however not possible to set a *quantifiable* threshold based on both the information available for bromide and the general uncertainties related to setting a threshold for endocrine-disruptive substances.
b) Already established reference values from other institutions are not appropriate for use in assessing the level of risk against the endocrine disruptive properties of bromide as they are established based on evaluation of the acute neurotoxic effects of bromide and do not focus on its endocrine disruptive effects.
c) Bromide is an essential trace element for human life and development, and internal tissue/blood bromide levels are within a defined range. It is however not possible to determine the minimum internal levels of bromide essential for human life.
d) The contribution of PT4 DBNPA-derived bromide to the average daily dietary bromide consumption is within the natural variation in daily dietary consumption considering the UK 1997 Total Diet Study reference value. Specifically, exposure from PT4 DBNPA-derived bromide contributes to the average daily dietary exposure of the general population by 0.03-1.33 % and the primary user by 5.1 % if considering this study. Although this study was performed over two decades ago, the 2010-2019 European Union reports on pesticide residues in food confirm that the daily bromide dietary intake has not declined since the period in which the UK 1997 Total Diet Study was conducted, making the reference value relevant for use in the risk assessment.
e) The adjusted upper and middle bound average daily intakes reported in the 2019 European Union report on pesticide residues in food confirms that the contribution of PT4 DBNPA-derived bromide

to be a fraction of the already daily bromide intake. Specifically, exposure from PT4 DBNPA-derived bromide contributes to the average daily dietary exposure of the general population by 0.02-1.1 % and the primary user by 4 % considering the middle bound average daily dietary intake and of the general population by 0.01-0.6 % and the primary user by 2.1 % considering the upper bound average daily dietary intake.

f) Use of the lower bound average daily intake reported in the 2019 EFSA report results in PT4 DBNPA-derived bromide contributing substantially to the daily dietary intake for the primary user. Specifically, exposure from PT4 DBNPA-derived bromide contributes to the average daily dietary exposure of the general population by 0.2-6.6 % and the primary user by 25 % considering the lower bound average daily dietary exposure.
g) Only automated transfer of the reference product into closed systems is considered relevant for exposure calculation for the primary user. The use of the input value for dermal and inhalation exposure is a worst case assumption, as it would otherwise be considered negligible. Furthermore, the primary user wears coveralls, gloves and respiratory equipment due to local effects of DBNPA. If the primary user should be exposed to DBNPA, the local effects would manifest before any systemic effect (including the endocrine disrupting effects), considering that the local effects of DBNPA have an immediate onset.
h) The calculated secondary exposure of the general public via food (bottles) is likewise highly unrealistic, as bottles are rinsed after disinfection with the PT4 DBNPA reference product. The scenario was originally included in the DBNPA CAR for PT4 as no measurements of the actual residues within the bottles were available, but it is clearly stated in the original assessment that this exposure is highly unrealistic. More data can be submitted in order to demonstrate the relevance and effectiveness of this rinsing step at the product authorisation stage.

Identification and discussion of uncertainties related to the conclusion

Overall, most of the sub conclusions are of a type where a discussion of potential uncertainties are not required. Below is a detailed discussion of the sub conclusions and potential uncertainties within these conclusions:

a) As it was concluded that a threshold exists based on a limited number of studies and limited assessment of adequateness of these studies, there may be uncertainties related to this conclusion, but the conclusion was not forwarded and used in the risk assessment as a defined reference value against the exposure to PT4 DBNPA-derived bromide, and thus would not change the conclusion if disproven. Furthermore, in the assessment of whether or not a quantifiable threshold could be demonstrated, it was clear that too many uncertainties exist to set a quantifiable threshold.
b) In the assessment of the other already established reference values from other institutions, the conclusion again was to not use these as reference values based on several uncertainties within the data used for these assessment, therefore no uncertainty analysis is needed within this assessment.
c) A potential uncertainty is the use of the reference values from the UK 1997 Total Diet Study and the 2019 European Union report on pesticide residues in food against the exposure to PT4 DBNPA-derived bromide. If using the lower bound ADI from the 2019 report as a reference value (as presented in subsection f in the above conclusions), the exposure to DBNPA-derived bromide in PT4 would contribute to the ADI by up to 25 %. This is not within the natural variation of the average daily intake of bromide. But the lower bound ADI is only a part of the assessment of intake in the European Union 2019 report. It is a highly unlikely scenario, which must be assessed together with the middle and upper bound ADIs. As these values are adjusted, they are considered more realistic of the bromide intake, as they are adjusted specifically to take into account that bromide may be present in food crops at levels below limit of quantification (LOQ), but only in food crops where at least one sample is shown to contain bromide residues at levels above the LOQ. However, because the presentation of lower, middle and upper bound reference values in these reports is a result of uncertainty related to the measuring of bromide content in food crops, this is a potential uncertainty.

d) Other potential uncertainties is related to the actual exposure estimates calculated for DBNPA for the primary user and the general public, but as stated, the estimates are highly conservative (worst-case), and therefore any correction of uncertainties related to these would only result in decrease in exposure to DBNPA-derived bromide from use in PT4.

Overall, the potential uncertainties related to the risk assessment of DBNPA-derived bromide from the use in PT4 should not disregard the conclusions, as they are either in favor of the conclusion or of a magnitude in which the conclusions would not be changed.

4.2.5 Provide an opinion

A threshold exists for the endocrine disruptive effects of bromide. It is however not possible to establish a common quantifiable threshold for these effects. Considering the conclusions as stated in section 4.2.4 on the risk from ED properties related to human health, no endocrine disruptive effects in humans are expected from exposure to DBNPA-derived bromide from use in PT4, as this contribution to the average daily intake is within the natural variation and the exposure calculations for the representative uses of DBNPA in PT4 are overestimates.

Therefore, no unacceptable risks are associated with exposure to DBNPA-derived bromide from the use in PT4.

5. Risks for the environment

5.1 Setting a threshold – section 11(a)

For setting a threshold for non-target organisms in the environment, please see the discussion regarding uncertainties as listed in section 3 above. These uncertainties are relevant for both human health and the environment. Furthermore, in section 4.1 above several challenges are listed which relates to the human health assessment, and some of these can also be considered relevant for the non-target organisms in the environment.

As stated previously, there is at the moment no available methodology to establish a threshold for ED effects and furthermore, there is no agreement in the scientific community whether it exists.

In the attempt at setting an absolute threshold for ED effects for non-target organisms, it is necessary to ensure all trophic levels are protected. Furthermore, such a threshold would also need to cover organisms living in different environmental compartments. Due to the lack of methodology on this matter, it is uncertain what data package would be needed to cover these aspects.

It is relevant to consider the species but also the most sensitive life stages that should be tested as well as which endpoints need to be measured. These might be different between the species. Considerations should also be done in terms of for which modality the ED effect has been observed, and whether there is a difference in the data package needed.

These considerations for relevant data are necessary for the entire data package that needs to be available to cover the environment as a whole, but it is uncertain if and how it is possible to choose a most sensitive NTO species, as they are not directly comparable. At the moment, it is not clear how this should be done for endocrine disruption and therefore the eCA does not consider it appropriate to establish a threshold as it would be highly uncertain whether the most sensitive species would be protected. This needs to be the subject of a more general discussion on the matter as the OECD GD 150 outline fish as the only aquatic organisms, for which tests are available to provide information on the EATS modalities. The endocrine system is complex, and there is a lack of knowledge on this for environmental organisms, especially for invertebrates.

In some areas of environmental hazard assessment, assessment factors are implemented in order to take into consideration the uncertainties related to establishing a limit value for the environment, which could also potentially be relevant for ED effects. However, as stated earlier for ED effects there is not knowledge

or guidance on how to set a threshold and in this regard also how assessment factors could be used for this exercise.

For bromide specifically, a threshold must exist since it is a naturally occurring substance. The studies submitted for the considerations of a threshold were limited and the two fish species have not been studied under the same conditions, i.e. different life stage and length of the studies. A study on African clawed frog (*Xenopus laevis)* was also submitted.

It is not clear how the different endpoints in the studies can be compared to define the most sensitive species in terms of ED effects, of those species for which data is available. The studies available from literature were not OECD guideline studies and they are generally not designed to obtain information on ED adversity or activity.

The two fish species tested showed different results, but were also tested in two different studies and more importantly, at two different life stages. Furthermore, how this relates to the population of the non-target organisms in the environment is challenging to explain.

Lastly, it is also relevant to consider that for the hazard assessment of the ED for non-target organisms, the data package can be very differing. For some substances (like DBNPA) the conclusion is based on the population relevance of the conclusion from the human health ED hazard assessment. For other substances, the conclusion might be based on ED relevant data for the environment, when the active substance is not ED for mammals. Therefore, the challenges of setting a threshold for ED effects could be different for these cases.

Based on the considerations mentioned above, it is concluded that despite the probable existence of a threshold for ED effects of bromide, there are at the moment too many uncertainties, which hinder the determination of an absolute threshold for the ED effects of the substance on a scientifically sound basis. A harmonised methodology is essential in attempting to establish a threshold for ED effects.

5.2 Background levels – section 11(b)

Bromide is a naturally occurring substance in the environment. Therefore, the mandate requests to determine the background concentration of bromide in the environment.

The bromide ions move as quickly as water in soil, as they do not absorb to negatively charged constituents of the solids (Flury & Papritz, 1993). As it is not expected that bromide absorbs to soil or sediment, these compartments will not be included in the assessment of this mandate.
Different active substances releasing active bromine is under evaluation under the BPR at the moment. In the draft assessments for the active substance active bromine generated from sodium bromide and sodium hypochlorite, these compartments are not considered necessary to be included in the exposure assessment, and all bromide released from the STP is assumed to be discharged to surface water, due to the intrinsic properties of bromide. The indirect emission to soil from sludge application is considered negligible. It should be highlighted that these assessment reports from are at the moment a draft version. Bromoacetic acid in PT4 is approved and in a similar manner, the assessment of bromide assumes that all bromide in the STP is released to the water phase without distribution to soil or sediment. The eCA agrees with these considerations and the assessment of bromide in this mandate has been performed in a similar manner. Therefore, only the surface water compartment is considered also when investigating the background concentration.

Bromine can be found in different forms in the crust of the earth as well as in the sea (WHO, 2018b). The concentration of bromide in the environment varies greatly throughout the environment and is highly dependent on the distance to the sea, as the sea is the greatest source of naturally occurring bromide (Flury & Papritz, 1993). Thus, aquatic environments close to the sea usually have a higher bromide content (WHO, 2018b) (Flury & Papritz, 1993).

Furthermore, the concentration of bromide can be subject to seasonal fluctuations and can change as a result of e.g. drought or pollution (WHO, 2017). Other natural processes that can affect the bromide concentration in fresh water are salt water intrusion and water from special geological formations. Also anthropogenic sources such as mining and chemical production can contribute to increased concentration of bromide (von Gunten, 2003). Anthropogenic sources will be discussed further below.

In seawater, the concentration of bromide is in the range from 65 mg/L to over 80 mg/L. In fresh water the concentration of naturally occurring bromide is lower, typically ranging from trace amounts to about 0.5 mg/L, but are highly variable (10–1000 µg/L) as also stated above (WHO, 2018b). The WHO did not establish a drinking water guideline value for bromide, explaining that the substance occurs in drinking water in concentrations well below those of health concerns (WHO, 2017). This is considered further in the Human Health assessment.

The eCA received a literature search on the background concentration of bromide in the environment. All environmental compartments were included, but due to reasons explained above, only concentrations in freshwater is presented in table 5.2-1.

In 1993 Flury & Papritz made a literature review concerning the environmental concentration and the toxicity of bromide. The authors categorised the typical mean concentration of bromide in freshwater to be between 0.014 and 0.2 mg/L, although the location of these measurements are not listed. Vanbriesen, (n.d.) included this information and reported the measurements to be from inland rivers and lakes in the USA. As the concentration of bromide in freshwater is dependent of the distance to the sea, the measurements could represent a worst case situation and therefore be of interest despite the measurements being from outside the European Union.

In a study by Von Gunten (2003) information from literature was compiled on the concentration of bromide in water works. Based on this review that the WHO determines the background concentration of bromide in the surface water of trace amounts to 0.5 mg/L (WHO, 2018b).

Table 5.2-1. Results from literature search on the background concentration of bromide in freshwater.

Reference	Key finding	Bromide concentration in freshwater
Flury & Papritz, 1993	The Br or Br- concentrations in freshwater usually are very small. The mean Bromine concentrations typical of freshwater are 0.014-0.2mg/kg. Data on the concentration of Br- in groundwater were reported. At some places near the coast values up to 2.26 mg Br/kg were determined. The large concentrations were thought to be the result of the infiltration of seawater into the aquifers because the ratio of CI- to Br- in the groundwater was close to the value typical of seawater. The Br- concentration in rain water is usually less than 0.01 g Br-/m3. The larger values from coastal areas suggest that seaborne aerosols are the main natural source of Br in terrestrial ecosystems.	- Freshwater (typical mean, USA): 0.014-0.2 mg/kg (or 0.014-0.2 mg/L) - Groundwater: 0.026 - 2.26 mg/kg (higher values near coastal areas) - Springs (Sweden): 0.016-0.08 g/m3 - Lake (Sweden): 0.024-0.24 g/m3 - River (Sweden): <0.008-0.07 g/m3 - River (USA): 0.2-0.3 g/m3 - River (Great Britain): 0.08-0.11 g/m3 - River (Great Britain): 0.09-0.1 g/m3 - River (Netherlands): 0.18 g/m3 - River (Netherlands): 0.27 g/m3 - River (Netherlands): 0.05 g/m3 - River (Netherlands): 0.7 g/m3 - Rain: <0.01 g/m3 (higher values up to 1 g/m3 near coastal areas)
WHO, 2009	Bromide levels in natural waters are highly variable (10–1000 µg/L), although typically range from trace amounts to approximately 0.5 mg/L	Natural water: 10–1000 µg/L (or 0.01-1 mg/L)
Von Gunten, 2003	Surveys on bromate formation in ozonation plants in numerous European countries and the USA have been carried out for water works under standard	France: 12-658 ug Br^-/L France: <20-200 ug Br^-/L Germany: 30-150 ug Br^-/L Switzerland: <5-50 ug Br^-/L USA: 2-180 ug Br^-/L

	treatment conditions (grab samples)	
Naily & Sudaryanto, 2018	The concentration of bromide in water is mostly < 1 mg/L	Freshwater: <1 mg/L
Good & VanBriesen, 2019	An analysis of Information Collection Rule (ICR) data (collected in 1997−1998) reported a range of below detection (<20 µg/L) to 2230 µg/L, with a median of 36 µg/L and a mean of 69 µg/L, for all water sources. A separate ICR data analysis reported a median of 30 µg/L and mean of 60 µg/L specifically for surface water sources.	All water sources: median of 36 µg/L (or 0.036 mg/L) and a mean of 69 µg/L (0.069 mg/L) Freshwater: median of 30 µg/L (0.03 mg/L) and mean of 60 µg/L (or 0.06 mg/L) USA
University of Georgia, 2017	Bromide concentrations in surface waters in the United States have typically been quite low, with average values inland ranging from 0.014-0.2 mg/L.	Inland groundwater: 0.0032 to 0.058 mg/L Inland fresh surface waters in USA: 0.014-0.2 mg/L
Merlob, 2007	Study is confidential	Jordan river: 1.8 mg/L Israel's drinking water survey between 2001-2006: 1.5-2.3 mg/L
Criquet et al., 2012	Bromide concentrations were in the range of natural waters from 0.19 µM (15 µg/L) up to 6.25 µM (500 µg/L). Bromide concentration from different sources -Lake Zurich = 15 (µg/L) - Lake Greifensee = 50 (µg/L) - North West Reservoir = 168 (µg/L) - Great Southern River = 412 (µg/L) - Great Southern Reservoir = 400 (µg/L)	**Table 1. Natural Water Characteristics** DOC (mg C/L) / SUVA (L/mg C·m) / I^- (µg/L) / Br^- (µg/L) Lake Zurich: 1.2 / 2.6 / <10 / 15 Lake Greifensee: 3.5 / 1.8 / <10 / 50 North West Reservoir: 2.8 / 1.7 / 31 / 168 Great Southern River: 12.0 / 4.1 / 17 / 412 Great Southern Reservoir: 20.0 / 4.9 / <10 / 400

FOREGS (Salminen, et al., 2005) collected samples of various chemicals in the different environmental compartments throughout Europe in the late 1990s to early 2000s. The freshwater samples were taken from streams of small, second order, drainage basins (<100 km^2). The dataset consists of several hundred of data points, which also include coordinates to the sampling sites. The eCA checked the location of several randomly chosen data points, and these are indeed small sized water bodies. The results support that the bromide concentration is generally low, but with large variations. It is also stated that due to poor analytical performance, a reliable discussion of the bromide distribution is not possible. As a consequence the data will not be used further than to support that the bromide concentration in what would be considered pristine environments is low.

Impact on background concentration from other anthropogenic influences

Flury and Papritz (1993) also included information on concentrations of bromide in known polluted areas. At the time of this review the three major anthropogenic sources of bromide in the environment was mining, emissions from leaded fuels and agriculture (fertilizers and pesticides), although bromide is used in many other industries and products as well. Information on polluted surface water areas in Europe from the review is included in table 5.2-2.

Table 5.2-2. Bromide concentrations in European freshwater as a result of anthropogenic activities from Flury & Papritz, 1993.

Area	**Source**	**Br^- concentration (g/m3)**
River, Germany	Mining	0.35
River, Germany	Mining	1-1.5
River, Spain	Mining	1-3.5
Water course in polder, Netherlands	Horticulture	Up to 8
Water course in polder, Netherlands	Horticulture	Up to 45

As also mentioned in section 4.2.3 methyl bromide was used as a pesticide for soil fumigation at this time, and the study attributes the pollution in the Netherlands in table 5.2-2 above, to be a result of this use.
Vanbriesen, n.d. state that bromide is also present is wastewater from the coal, oil and gas industries today. Furthermore, the report mentions other industries, which also use bromide, e.g. for dyes, pharmaceuticals and flame retardants. The substance is also used as a non-reactive tracer in environmental studies.

The industrial use of bromide often leads to bromide being released into surface waters. Bromide concentrations and sources in surface waters in Switzerland (used as a model for industrialized countries) were investigated by Soltermann et al., 2016. The study refers to previous measurements of Swiss drinking water resources showing bromide concentration of drinking water resources from 85 water works in Switzerland to be generally low at around <20 ug/L in rural, surface and spring water. Furthermore, bromide concentration was found to reach 55 ug/L in groundwater and surface waters, which were influenced by anthropogenic sources.

Three different major Swiss rivers were investigated by Soltermann et al. (2016) for bromide content compared to the previous drinking water resource measurements and the impact from anthropogenic sources were investigated. The three locations sites and their representation were:

- Weil am Rhein, which cover northern Switzerland and smaller areas of Germany and Austria. It covers 67 % of Swiss surface and 78 of the population and includes major industrial areas of Basel and Zurich.
- Brugg, which represent a regular industrial share.
- Rekingen, which represent limited industrial activity.

The measurements taken at Rekingen were the only measurements, which showed bromide concentrations similar to those from the 2003 study. The measurements from the other two sampling sites showed bromide concentrations of approx. 300 ug/L and more variable.
The study also considered the annual load of bromide in the three sampling sites, which also differed. The annual load of bromide in Weil am Rhein was 2000-3000 t/y, Brugg was 500 t/y and Rekingen was 100 t/y. These values for bromide loads are not proportionate to the size of the area or population and therefore the authors conclude that local industry or natural sources influence these loads.

The authors estimated the sources of the bromide load for Weil am Rhein in 2014, which is considered a year with a lower load (approx. 2000 t/y) as follows:

Figure 5.2-1. Estimation of sources of bromide in an annual load of 2000 t/y for Weil am Rhein in 2014 (Soltermann et al., 2016)

bromide sources	bromide load (t a^{-1})	%
municipal waste incinerators	363	18
special waste industry	271	13
chemical industry	1069	52
precipitation and geogenic	160	8
various small sources	182	9
landfills	(30)	(1.5)
agriculture	(30)	(1.5)
biocides	(40)	(2.0)
human excrement	(17)	(0.8)
road and industrial salt	(5)	(0.2)
input from Germany and Austria	(60)	(2.9)
total	2045	100

[a]Values in parentheses are bromide loads and shares of the subcategories that are summarized as various small sources.

Concentration of bromide in waste water treatment plants effluent is also investigated by Soltermann et al. (2016) although the information on this is generally scarce. Data from eight waste water treatment plants (WWTP) were available which showed variations in bromide concentration between 0.006 to 48 mg/L. Data showed a low concentration of bromide (<0.1 mg/L) in mainly municipal wastewaters (representing the majority of WWTP), slightly higher (0.1-0.3 mg/L) in wastewaters with industrial influences and clearly higher (>0.4 mg/L) in WWTP with waste incinerators or with wastewater exclusively from industrial sources.
The study further focuses on drinking water quality in Switzerland, which is outside the scope of this mandate.

The eCA was informed that it is important to consider that industrial effluents are not released into pristine aquatic environments, where bromide levels are much lower, as also reflecteda in literature. As also explained by Soltermann et al. (2016), these local more industrialised environments generally have a higher background concentration of bromide.

The toxicity of bromide to aquatic organisms and the ability of organisms to adapt to the natural variation of bromide has not been taken into consideration for this section of the mandate. The mandate strictly requests the determination of the background level and therefore the eCA have focused on answering this. The eCA did however receive a study (DeGraeve & Ward, 1977) which investigated the ability of two fish species (fathead minnow and lake trout) to adapt to increasing concentrations of chlorinated and chlorobrominated effluents. The conclusion is presented here for completeness sake. The authors concluded that fish with previous exposure were able to tolerate higher concentrations over a longer period than organisms without previous exposure.

5.3 Exposure of NTO to DBNPA-derived bromide – section 11(c)

The mandate from the Commission requires the eCA to determine the exposure of non-target organisms to DBNPA-derived bromide from the PT4 use specifically. Any other use of DBNPA and/or bromide will not be included in this exposure assessment, which is in line with how active substance assessments are performed under the BPR.

Experience from other biocidal active substances assessments of naturally occurring substances

Although this assessment is the first of its kind in terms taking ED effects into consideration in an exposure and risk assessment of a naturally occurring substance, it is not the first evaluation of a naturally occurring substance in general under the BPR. Although outside the scope of this mandate, the considerations of how previous assessments were performed was raised to the eCA. Therefore, a brief

presentation of assessments of a naturally occurring biocidal active substances and a metabolite are presented below. It is important to note that the assessments did not consider the ED properties, as the substances were approved prior to the setting of the ED criteria.

The active substance bromoacetic acid in PT4 is approved and this assessment included an assessment of the risk to freshwater from bromide. Scientific literature was used to establish a PNEC value of 0.22 mg/L and the AR refers to the background value of 0.27 mg/L in the Netherlands from Flury & Papritz (1993) to support the use of this PNEC value.

Iodine is another naturally occurring substance evaluated under the BPR, in this case for PT 1, 3, 4, and 22. In the risk assessment of this substance, the PEC/PNEC value was above 1 for some uses. Therefore, the PEC was compared to the background concentration to show the PEC being within the natural variation of iodine in the environment. Therefore, the risk was considered acceptable.

Exposure assessment of DBNPA in PT4

The uses calculated are disinfection of food processing vessels (e.g. industrial mayonnaise or yogurt producing facilities, fermenters for beer or other fermented products), which are the uses calculated for the representative product in the PT4 use on the CAR for DBNPA. Exposure from any other sources of DBNPA is not included.

The mixing and loading process takes place in completely closed systems and therefore, the environmental exposure during mixing and loading is considered to be negligible compared to the actual application of DBNPA. The emission estimations for the use of DBNPA in PT4 have been determined using two different scenarios (a tonnage based scenario and a consumption based scenario) and a tiered approach.

The relevant route of exposure is direct exposure to STP and subsequently indirect exposure to surface water (including sediment) via STP effluent; to soil (including groundwater) via STP sludge application to land. The exposure calculations take into consideration the degradation of DBNPA in the STP. However, when considering the exposure to the environmental compartments from DBNPA-derived bromide, it is necessary to look at the concentration of DBNPA at the influent to the STP. It is not relevant to consider any degradation of DBNPA in the sewer system, as this would not decrease the amount of DBNPA-derived bromide, since bromide will not degrade further. The concentration of DBNPA in the influent to the STP would be considered as the worst-case of DBNPA-derived bromide from the uses of the representative product. Concentrations of DBNPA are presented in table 5.3-1.

Table 5.3-1. Concentration of DBNPA in the representative uses. Values are from DocIIB of DBNPA in PT4.

Scenario	**Description**	**DBNPA**
Tonnage based scenario: ESD for PT4: Assessment of entire plants off-site treatment.	Food processing vessels. Based on amount of DBNPA (4000 ppm) supported by the efficacy data submitted	0.286 mg/l (influent concentration of active substance in the off-site STP)
Tonnage based scenario: ESD for PT4: Assessment of entire plants off-site treatment.	Bottle washing. Based on amount of DBNPA (4000 ppm) supported by the efficacy data submitted.	2.0 mg/l (influent concentration of active substance in the off-site STP)
Consumption based scenario.	Food processing vessels or bottle washing (4 kg for both food vessels and bottle washing.	4 kg/d (emission to waste water)

The consumption based approach (i.e. scenario 2) is the worst-case according to the final CAR of DBNPA. However, for the sake of completeness both scenarios are calculated for bromide.

Based on the properties of bromide, c.f. section 4.2, the substance is expected to be found in the water after the STP treatment. According to the exposure section of the dCARs for active bromine generated from sodium bromide and sodium hypochlorite provided by the NL CA, it is therefore assumed that all bromide released to a STP will be discharged to surface water. Indirect emission to soil via spreading of sludge is considered to be negligible. This will also be the case for the calculations of exposure to DBNPA-derived bromide. This means that from the STP 100 % of the bromide is assumed to be discharged to surface water.

In order to calculate the exposure of non-target organisms to DBNPA-derived bromide, a 100 % conversion of DBNPA to bromide is assumed as a worst-case. DBNPA consists of two bromide-atoms,

The following parameters are used for the calculations:

- Molecular weight DBNPA: 241 g/mole
- Molecular weight of bromide: 79.904 g/mole
- DBNPA-derived bromine in STPinfluent: (79.904*2)/241 * STPinfluent of DBNPA.
- Dilution factor 10 (from STP to surface water)

The conversion of DBNPA to bromide for the representative uses of DBNPA in PT4 is presented in table 5.3-2 below.

Table 5.3-2. Concentrations of DBNPA in use (table 5.3-1) converted to bromide by 100 % transformation.

Scenario	**Description**	**Bromide calculations in STP**
Tonnage based scenario: ESD for PT4: Assessment of entire plants off-site treatment.	Food processing vessels. Based on amount of DBNPA (4000 ppm).	DBNPA: 0.286 mg/l (influent concentration of active substance in the off-site STP) Bromide: (79.904*2)/241 * 0.286 mg/l = 0.190 mg/L
Tonnage based scenario: ESD for PT4: Assessment of entire plants off-site treatment.	Bottle washing. Based on amount of DBNPA (4000 ppm).	DBNPA: 2.0 mg/l (influent concentration of active substance in the off-site STP) Bromide: (79.904*2)/241 * 2.0 mg/l = 1.326 mg/L
Consumption based scenario.	Food processing vessels or bottle washing (4 kg for both food vessels and bottle washing.	DBNPA: 4 kg/d (the local daily emission to waste water when degradation in the application phase was not taken into account) Bromide: (79.904*2)/241 * 4.0 kg/d = 2.652 kg/d

To calculate bromide from the effluent of the STP to the surface water in the tonnage based approach equation 48 from the Guidance on the BPR: Volume IV Environment, Assessment & Evaluation (Parts B+C) is applied. This is considered the local concentration in surface water during an emission episode.

To calculate bromide in the effluent of the STP to the surface water in the consumption based approach, equations 35 and 36 of the Guidance on the BPR: Volume IV Environment, Assessment & Evaluation (Parts B+C) is used. A standard dilution factor of 10 is applied to consider the dilution from STP to surface water.

The resulting concentrations of bromide in local surface water are presented in table 5.3-3.

Table 5.3-3. Concentration of bromide in the surface water from the use of DBNPA in PT4.

	Concentration in surface water (mg Br^-/L)
Tonnage based scenario: Food processing vessels	0.019

Tonnage based scenario: Bottle washing	0.133
Consumption based scenario	0.133

In the DocIIB for DBNPA, the consumption based approach is considered to be the worst case scenario for exposure to the environment and this scenario will thus be used in this risk assessment.

Worst case scenario (highest use concentration, 100 % transformation to bromide, 100 % bromide to surface water from STP) result in a concentration in local surface water of DBNPA-derived bromide of 0.133 mg/L.

5.4 Level of risks to the environment – section 11(d)

In section 5.1 a number of uncertainties is described related to setting a threshold of the ED properties of bromide for non-target organisms in the environment. Due to the uncertainties, a lack of guidance/methodology on how to address these uncertainties, and the data package needed in order to establish a threshold, it is concluded that it is not possible to set such a threshold for the ED properties of bromide for the non-target organisms in the environment. As bromide is naturally occurring in the environment, a threshold for the ED effects must exists, however as a consequence of the uncertainties, it is not possible to conduct a quantitative assessment of the risks to the environment associated with these properties.

Instead, the eCA proceeded to a qualitative assessment taking into consideration the background concentration of bromide, as requested in the mandate. Furthermore, the calculated exposure of bromide following the representative use of DBNPA in PT4 was considered. Due to having an exact exposure concentration compared to information gathered on the background concentration of bromide in the environment, it would be more appropriate to refer to this assessment as a "semi-quantitative" assessment instead of "qualitative" as expressed in the mandate.

The literature compiled for meeting the requests of the mandate showed limited information available on the background concentration of bromide in the environment. Because of the scarcity of information, values from Europe as well as outside Europe was presented in Table 5.2-1, which would be considered the concentrations in pristine environments. As shown in the table, the concentration of bromide in the aquatic environment varied greatly in the data from literature, from trace amounts to 0.7 mg/L in Europe. Furthermore, the literature described that many natural factors can contribute to the concentrations of bromide. Such factors are e.g. the geology of the area, seasonal fluctuations, drought, but the greatest source of naturally occurring bromide is the sea. Therefore, the concentration of naturally occurring bromide in aquatic environments increase with increasing distance to the sea. Due to this variation in the bromide concentrations, a single fixed value for the bromide concentration in European surface waters was not established.

From the literature, it is also evident that there are many anthropogenic sources to bromide in the surface waters. Literature describes e.g. pollution, chemical industry, mining as contributors to bromide emissions. Bromide is used in several different industries such as pharmaceuticals, oil and gas industry, as flame-retardants etc. Information on anthropogenic sources to bromide in surface water is also scarce, especially taking into consideration that this information would need to be from Europe in order to reflect the industries as well as European practices. Furthermore, the information would also need to be relatively new in order to reflect current standards and legislations.

A study from 2016 investigated the bromide concentration in Swiss surface waters in areas with different levels of anthropogenic activity. Measurements showed higher bromide concentrations in areas of regular

industrial activity and in areas of major industry, which also represents the majority of the population, compared to the area of limited industry. The authors furthermore estimated the sources of the annual load of bromide in the area of major industrial activity and the majority of the population in a load of 2000 t/y. This estimation showed that the three main contributors for bromide in the areas were chemical industry (52 %), municipal waste incinerators (18 %) and special waste industry (13%). It is estimated that the use of biocides contribute with 2 % of the annual bromide load.

Bromide concentrations are shown to be higher in areas affected by anthropogenic activities and the general biocides use is estimated to be a minor contributor compared to other sources of bromide. It is estimated that of the annual bromide load in an industrial area (with majority of population) 2 % of the bromide it attributed to a general biocides use, i.e. not specifically DBNPA, but all biocides. The concentration in those areas were considered to be varied but with concentrations up to 300 ug/L.

The study of Switzerland can be considered a good indicator of the bromide exposure in general, as the study includes considerations of industry as well as residential areas and is relatively new (2016). Furthermore, as explained in literature the sea is the biggest natural source of bromide, and Switzerland might therefore be a good example, as natural concentrations of bromide is expected to be lower, as Switzerland is landlocked and therefore might present some of the lower natural bromide concentrations in Europe.

As stated above, the exposure of DBNPA-derived bromide from the PT4 use was 0.133 mg/L, which would be considered within the range of natural variation of bromide concentration in surface water found in literature and presented in section 5.2, but in the higher end of that variation. When comparing this exposure concentration to the measurements and information from the study of Switzerland, it is above the bromide concentration in rural areas with only limited industrial activity. The exposure concentration was below the concentration of bromide in the areas of regular industrial activity and of major industrial activity also representing the majority of the population. DBNPA in PT4 is to be used in industrial areas, and it would therefore be more relevant to compare the exposure to an area with regular or major industrial activity.

The data on background levels of bromide is challenging to work into the context of an assessment of an active substance under the BPR. Data is scarce, which makes it impossible to give a full picture of the bromide concentrations in all member states. Furthermore, the information available might not be sufficient to compare water bodies and the measurements might be taken in different years and/or time of the year. Therefore, the data can be used to give a more general picture of the variation of naturally occurring bromide.

Overall, the exposure of DBNPA-derived bromide from PT4 use results in a concentration in the surface waters, which can be considered within the natural variation, but in the higher end of the reported values. This corresponds well with the Swiss study were the bromide concentrations from DBNPA in PT4 would exceed concentration of bromide in areas with limited industry. In the areas with regular or major industry, the concentration of DBNPA in PT4 would be within the bromide concentrations found in such areas and below the highest concentrations reported.
The estimation of annual load show only a small fraction of bromide released in the area is from a general biocides use. The impact of DBNPA-derived bromide from industrial use in PT4 would be considered to be minor compared to other industrial activities.

The use of DBNPA in PT4 would result in exposure to the environment through emissions from the STP to the surface water. The applicant informed the eCA that it can be expected that release from the STP will

not be to pristine environments. At the ENV WG several members raised their concern about the release from STP to surface water, due to the lower bromide concentrations reported for some pristine water bodies. Usually this aspect is not considered further under the assessment of an active substance under the BPR, and the eCA does not have the possibility to look into this aspect for all member states. The eCA did however look into what considerations needs to be done for release of industrial wastewater in Denmark. From national legislation it is not permitted to add polluting substances to the aquatic environment, however after obtaining a permission, wastewater can be emitted to streams, lakes and the sea. The permission is usually obtained from the relevant municipality, but in some cases, it is the Danish Environmental Protection Agency. Most often, a company need a permission to connect to the wastewater treatment plant and the wastewater supply company need a permission to allow emission from the wastewater treatment plan. In an application for permission, sufficient information on wastewater quantity and environmentally harmful chemicals needs to be included. The municipality decides on the information needed. There might be specific requirements for emission of certain substances in order to meet water quality criteria. For industrial wastewater it might be required to pre-treat the wastewater to ensure BAT is used and that aquatic environments will not be influenced in an unacceptable manner.

The Water Framework Directive is partly implemented in the Danish legislation on water planning. Quality goal for water bodies are established in “vandområdeplaner” and the municipalities have to consider these plans when permitting emissions of wastewater, and the emission cannot hinder meeting these goals. This can e.g. include considerations of cumulative releases to an aquatic environment. Although outside the scope of the assessment of an active substance under the BPR, this explanation shows that the application for permission of release of industrial wastewater need to consider the water body to which it will be emitted.

Identification and discussion of uncertainties related to the conclusion

As it was concluded that a threshold exists based on a limited number of studies and limited assessment of adequateness of these studies, there may be uncertainties related to this conclusion, but the conclusion was not forwarded and used in the risk assessment as a defined reference value against the exposure to PT4 DBNPA-derived bromide, and thus would not change the conclusion if disproven. Furthermore, in the assessment of whether or not a quantifiable threshold could be demonstrated, it was clear that too many uncertainties exist to set a quantifiable threshold.

In terms of the background concentration of bromide in the environment only a limited number of studies were available. If more information becomes available it could potentially be possible have a more complete understanding of the background concentrations in all European water bodies, but the large variety of bromide concentration would be expected to remain. Similarly, more information could become available on the anthropogenic sources of bromide, but it would also be expected that these would show a higher concentration of bromide in areas of industrial activity.

The data included in the assessment needed to be of relatively new character in order to reflect current European practices, legislations and standards. Therefore the data used on the assessment is considered to be adequate to conclude.

Other potential uncertainties is related to the actual exposure estimates calculated for DBNPA for the surface water, but as stated, the estimates are highly conservative (worst-case), and therefore any correction of uncertainties related to these would only result in decrease in exposure to DBNPA-derived bromide from use in PT4.

Overall, the potential uncertainties related to the risk assessment of DBNPA-derived bromide from the use in PT4 should not disregard the conclusions, as they are either in favour of the conclusion or of a magnitude in which the conclusions would not be changed.

5.4.1 Provide an opinion

Many different aspects have been considered in the assessment of the risk associated with the ED properties of bromide for NTOs in the environment. Although a threshold for the ED effects must exist due to the natural occurrence of bromide, it was not possible to quantify such a threshold.

The background concentrations of bromide varies greatly in the pristine aquatic environments and the concentration in surface water from the DBNPA use in PT4 would be within that natural range, but in the higher end. The concentration in water bodies in areas of regular to major industrial activity shows a higher concentration of bromide, which were also above the concentration in surface water from DBNPA use in PT4. Many other anthropogenic sources of bromide has been identified and the exposure from biocides is minor compared to other sources.

Since release to the environment of DBNPA occurs via wastewater from industrial use a risk related to ED properties cannot be excluded, however the risk could be considered tolerable when considering the other anthropogenic sources of bromide and the natural variation of bromide in the environment. In an area of industrial activity, the emission of bromide from DBNPA in PT4 to the environment would only contribute a fraction of the total bromide emission in the area.

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